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Original Communications

NORMAL AND CYSTIC STRUCTURES OF THE BROAD LIGAMENT*†

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THE literature on broad ligament cysts was reviewed in an attempt to find or to formulate an accurate classification of these structures. The results were unexpectedly confusing. The terminology used by various authors was highly individualistic. The following names were noted: paratubal cyst, parovarian (also para-ovarian, parovarial) cyst, Wolffian cyst, intraligamentous cyst, Kobelt's cyst, epoophoral cyst, fimbrial cyst, junctional cyst. The remnants of the embryonic mesonephros (Wolffian body), from which most authors believe these cysts to be derived, were called variously: Wolffian body, epoophoron, Organ of Rosenmüller, Kobelt's tubules, parovarium, parovarial tubules. Anatomical descriptions, particularly as to histology, were equally varied. Opinions on histogenesis were less diverse but were frequently beclouded by two factors: (1) There seems to be little specific knowledge of the structures that are present in the normal broad ligament. (2) Of even greater importance were the contradictory and frequently inadequate or even erroneous concepts of the embryonic development of broad ligament structures. One of the erroneous concepts was traced to the assumption that details in the embryonic development of the rete in the tortoise were directly applicable to man.

The terminologic welter, histologic mélange, and embryologic diversities left us in a state of mind that could best be described as one of "chaotic confusion." It was, therefore, decided to study the embryonic development of broad ligament structures, the normal adult broad ligament, both in routine and in serial section, and, finally, the abnormal broad ligament. That portion of the study having to do with the histogenesis of broad ligament cysts will be presented here. A simple classification based on histogenesis will be proposed.

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The data will not include a statistical study, nor consideration of tumors of mesodermal origin. It will be concerned with epithelial elements normally found in the broad ligament and retention cysts arising therefrom.

Materials

Fourteen serially sectioned specimens from embryos and newborn were studied. These were obtained from 14, 22, 24, 27, 80, 80, 95, and 95 mm. embryos; 5, 7, and 8 month fetuses; and three newborn infants.

Adult material was obtained from routine blocks of 598 normal and pathologic broad ligaments, tubes, and ovaries. This figure refers to the number of operative patients. In some instances, both broad ligaments were available for study. In addition, the lateral half of eleven broad ligaments was serially sectioned at 10 microns. These preparations include the base of the ovary and the mesosalpingeal portion of the tube. The remainder of the block from four routine preparations was also serially sectioned.

Some of the details and differential points to be considered later are based on finer histologic features. They necessitate microscopic preparations of high quality. The routine pathology slides of some institutions, at least, would not meet this specification. Autolysis and desiccation result from excessive delay in placing the operative specimen in the fixative. Harsh fixatives, such as the commonly used 10 per cent formalin, cause undue shrinkage and distort cell structure. Rushing tissues through an Autotechnicon and careless work by technicians cause further damage.

The older routine sections used in this study were not prepared in an ideal manner, since they were fixed in 10 per cent formalin. All the more recent tissues, however, (approximately 150 operative specimens) were immediately placed in Bouin's fluid in the operating room. Microscopic preparations were made by Miss Mildred Milligan, to whose technical competency and artistic skill part of the credit for this study must be attributed. Credit must also be given to the equally competent Mrs. Karen Gustafson, who prepared the majority of the serial sections.

The stains used were: routine hematoxylin and eosin, the Milligan Stain (Milligan 1946), iron hematoxylin-mucicarmine, and glycogen stains. Hematoxylin and eosin is satisfactory for routine purposes but is unsatisfactory for some histologic details.

Embryology and Definition of Terms

Mesonephric Structures.—In the embryo, the mesonephric duct and some 80 mesonephric tubules are part of a urinary excretory apparatus, the mesonephros. With formation of the definitive or metanephric kidney, the mesonephros almost completely disappears. However, the caudal one-third or one-fourth of the mesonephric duct and the 10 to 15 mesonephric tubules connected with the cranial part of the duct remnant are preserved. In the male, these remaining tubules and duct become the spermatic duct system. In the female, the mesonephric tubules and that part of the duct in connection with them are consistently preserved and persist as such throughout adult life. The tubules are grouped together and extend from the most lateral portion of the hilum of the ovary toward the tube. Near the tube, they communicate with the mesonephric duct which runs parallel to the course of the tube.

The mesonephric tubules and duct found in the adult broad ligament actually represent a continued existence of the same structures found in the

embryo. We shall, therefore, refer to them as mesonephric tubules and mesonephric duct. We see no reason to call them by any other of the confusing names with which they have been saddled (Table I). We object in particular to the use of a man's name (no matter how illustrious) in designating anatomic or histologic structures or pathologic conditions. The name of a structure should, if possible, have functional, histogenic, or at least morphologic, significance. It would appear better to avoid confusion than to add to it by the use of personalized nomenclature.

Paramesonephric Duct.—Our bias against using the names of individuals for structures also extends to "Müllerian duct." We prefer a term used by

TABLE I

PROPOSED TERMINOLOGY	COMMONLY USED TERMINOLOGY
Mesonephric body	Wolffian body, organ of Rosenmüller, epoophoron, paroöphoron, parovarium, Kobelt's tubules, parovarial tubules
Mesonephric duct	Wolffian duct, longitudinal tubule of epoophoron
Mesonephric tubules	Wolffian tubules, Kobelt's tubules, epoophoral tubules, transverse tubules of epoophoron
Paramesonephric duct	Müllerian duct
Oviduct Uterine tube	Fallopian tube
Accessory oviducts	Accessory Fallopian tubes

many modern embryologists, "paramesonephric duct." For "Fallopian tube," we shall use the anatomically preferable name, "uterine tube," or the functional term, "oviduct." The latter is a better descriptive name.

The paramesonephric duct is a latecomer compared to the mesonephric duct. The latter gets its start at about 4.5 mm., while the former does not develop until about 10.0 mm. (4 weeks and almost 6 weeks, respectively). This is fortunate, since the paramesonephric duct seems unable to differentiate as it should, without the mesonephric duct to guide it. It has long been known that absence of a kidney, in certain patients, is due to lack of development of mesonephric duct (normally the ureter must bud off from the mesonephric duct and reach the metanephric anlage for formation of the kidney). In these same patients, only the most lateral part of the tube is present, and the same side of the uterus is missing, so that it is unicornuate. Gruenwald (1941) has very beautifully demonstrated the cause for this. He interrupted the continuity of the mesonephric duct early in the development of the chick embryo. The later-developing paramesonephric duct never reached its normal destination (urogenital sinus). Its course was terminated at the area where the mesonephric duct had been severed. He has also demonstrated in the human being that the growing, advancing tip of the paramesonephric duct travels under the basement membrane of, and is guided in its course by, the already existent mesonephric duct.

As previously noted, the paramesonephric duct begins its development at about 10 mm. On the lateral surface and near the cranial end of the mesonephric body, a groove appears in a localized area of thickened epithelium.

This groove invaginates caudalward and into the stroma. The rapidly growing tip reaches and penetrates under the basement membrane of the mesonephric duct and continues its caudalward growth thereunder. This phenomenon is clearly evident in our own specimens (14, 22, 24, and 27 mm.). However, only the continuously growing tip is found under the basement membrane, the older and more cephalad part of the duct being just external to the basement membrane, and then, finally, separated from the mesonephric duct by intervening stromal cells.

The paramesonephric duct reaches its objective (the urogenital sinus) in this manner at about 30 mm. (approximately 9 weeks). When finally differentiated, the cranial one-third of the paramesonephric duct becomes the oviduct or uterine tube.

While the paramesonephric duct is coursing downward to reach the urogenital sinus, the fimbriae are being formed. This process is most clearly described by Felix in Kiebal and Malls' "Human Embryology" (1912). The original epithelial invagination forms the primary or definitive ostium of the tube. In the area surrounding this ostium, multiple secondary invaginations occur, grow downwards, develop a lumen, reach, and, finally, penetrate through to the lumen of the paramesonephric duct. These secondary invaginations en masse form the anlage of the fimbriae, which develop by a process of epithelial and then luminal coalescence.

The probable fate of secondary invaginations that do not contact the original paramesonephric duct, but continue their irresponsible way, unguided by the mesonephric duct, will be discussed in later sections.

I. Structures of the Normal Broad Ligament

Mesonephric Structures.—In the majority of gynecologic textbooks, the normal structures of the broad ligament are treated in a rather cavalier manner and dismissed from further consideration after a few cursory sentences or paragraphs. Frequently, however, a copy or "modification" of a drawing made in 1905 is included. This drawing had much artistic merit but, unfortunately, it portrays the mesonephric tubules as being fairly evenly spaced throughout the broad ligament. Actually, mesonephric tubules are not uniformly spaced throughout the broad ligament. Instead, the mesonephric tubules (with the exception of those inconstantly present, mesial to the vessels in the mesovarium [paroophoron]—with which we are not concerned) are found in a specific portion of the broad ligament. Normally, the ovarian blood vessels course through and occupy, in so doing, the middle third of the mesovarial area. The mesonephric tubules are closely grouped in the most lateral one-third of the mesovarium and extend up through the most lateral mesosalpingeal portions of the broad ligament. Various authors have previously reported this fact. (Kobelt, 1847, Duthie, 1924, Watkins, 1933.) It can easily be confirmed by inspecting the freshly removed ovary and broad ligament held up against a fairly strong light.

The mesonephric duct (Figs. 1 and 2) is found in microscopic sections fairly close to, but external to, the musculature of the oviduct. It is usually moderately convoluted, and several cross sections may therefore be seen in one slide. It has its own discrete muscular investment, with an unusual arrangement of inner longitudinal and outer circular fibers. The muscular layer is

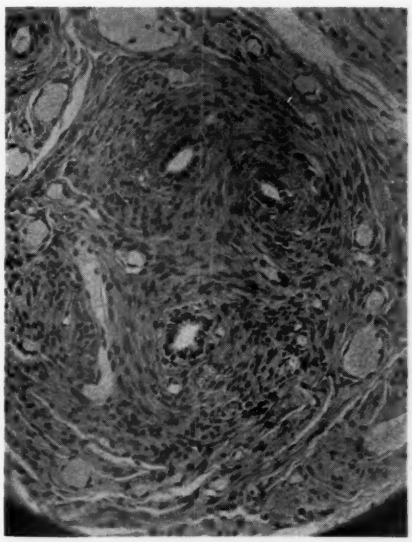

Fig. 1.—Several cross sections through a convoluted mesonephric duct. The muscle coats are well developed and the epithelium is simple cuboidal. ×600.

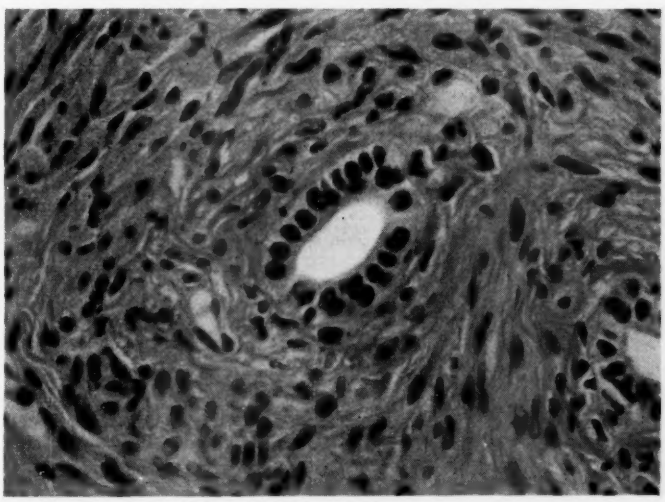

Fig. 2.—Mesonephric duct. Higher magnification of duct from Fig. 1. ×1995.

usually heavier than that of the mesonephric tubules. The duct epithelium in almost all of our specimens has been low cuboidal with mesially placed, moderately vesicular nuclei. In the few exceptions, the epithelium has been somewhat higher, with a tendency of the cytoplasm to "stream out" into the lumen. No cilia have been found in the duct epithelium.

The mesonephric tubules (Fig. 3) are usually more highly convoluted than the gently undulating mesonephric duct. Its musculature, according to Duthie (1924), also consists of an inner longitudinal and an outer circular layer. This has been true in most of our specimens, but not definitely demonstrable in others. Deep in the broad ligament (in the mesovarial area) as the mesonephric tubules near the rete, the muscular coat is lost.

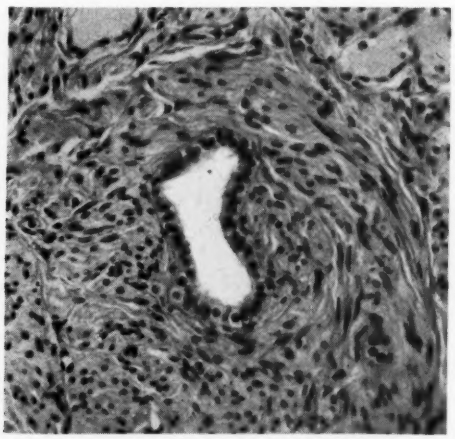

Fig. 3.—Mesonephric tubule. Note well-developed muscle sheath. Epithelium is more complex than in the mesonephric duct. See Fig. 7 for greater magnification. ×840.

The epithelium of the tubules is more specialized and more prominent than that of the duct. The cells, while low columnar or cuboidal, are quite large. Two types are present, ciliated and nonciliated. The cytoplasm of the ciliated cells stains very lightly; so much so that, occasionally, the cell looks vacuolated. Their nuclei are large, usually round, and centrally located in the cell. With an iron hematoxylin or a Milligan trichrome stain, the basal corpuscles of the cilia make a prominent darkly staining line just proximal to the luminal surface of the cell. The cilia are prominent with the above stains but are easily visible with routine hematoxylin and eosin stain.

The cytoplasm of the nonciliated cell stains more darkly and thus contrasts with that of the ciliated cell. Both types of cells are usually the same height, although the nonciliated cells may be somewhat narrower than the ciliated. The nuclei of the nonciliated cells are usually centrally placed and oval in shape, with granular chromatin. Occasionally these cells appear compressed and elongated.

This description of mesonephric tubule epithelium is applicable to a vast majority of tubules in both our routine and serially sectioned specimens. In a very few specimens, atypical, presumably hyperplastic epithelial changes have been noted. In four specimens, epithelium has been found that is identical to that of the male homologues (efferent tubules in one and conus epididymis in three). These atypical epithelia will not be discussed further in this presentation.

In the literature, descriptions of the epithelium of the mesonephric tubules are (to say the least) somewhat varied. The descriptions vary from simple cuboidal epithelium (Novak, 1947), cuboidal to columnar epithelium (Duthie, 1924), columnar epithelium (Cole, 1910), cuboidal to columnar epithelium with structures which look like cilia but are artifacts (Opocher, 1939, Lucchetti, 1937), cuboidal to columnar epithelium that may bear cilia (Piersol, 1916, Craig), to ciliated columnar epithelium (Doran, 1884). While some of these erroneous descriptions may be due to inadequate observations, it is believed that most are due to delayed fixation, use of harsh fixatives, or inadequate histologic technique.

Few observers have differentiated the epithelium of the mesonephric tubules from that of the duct. Doran, in the latter part of the last century, however, in his book on ovarian and broad ligament tumors, did this very clearly. While he erred in stating that the tubule epithelium consisted entirely of ciliated columnar cells, no one can criticize his description of the "simple cuboidal" epithelium lining the mesonephric duct.

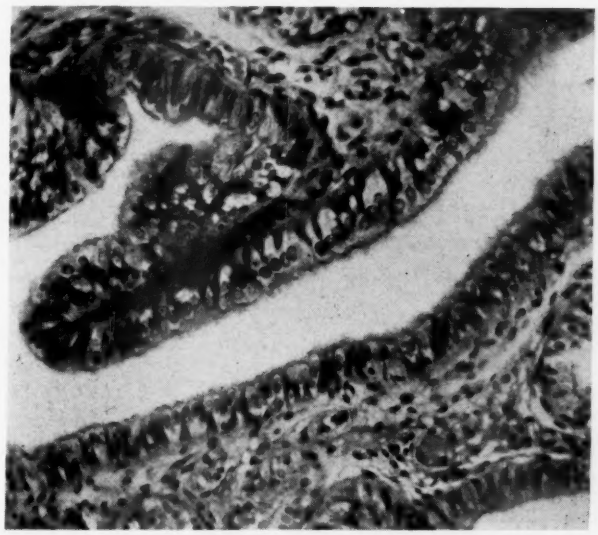

Fig. 4.—Normal oviduct epithelium in estrogenic phase. ×840.

Paramesonephric Derivatives.—The general anatomy of the oviduct will not be considered here. The histology of the epithelium (Fig. 4) is, however, pertinent. It is similar to the epithelium of the mesonephric tubules in that it contains both ciliated and nonciliated cells. The latter, in the oviduct, are commonly called "secretory cells." In addition, another type of cell has been described. This so-called peg cell, however, probably represents only a much squeezed and elongated secretory cell and will not be considered further.

The actual height and relative height of the secretory and ciliated cells vary with different stages of the menstrual cycle. During the estrogenic or preovulatory phase, the epithelium is quite high—all the cells being high columnar and of the same height. The luminal surface during this stage is, therefore, quite smooth and regular. In the progestational phase (secretory), the secretory cells are relatively higher than the ciliated cells. The latter at this stage are large, plump, low columnar cells. The secretory cells are still elongated. However, they have much less cytoplasm, and their nuclei may project into the lumen, covered by a thin layer of cytoplasm. During early menses (and pregnancy)

the epithelium is much lower, the luminal surface even more irregular, with practically bare secretory nuclei projecting well above the surface of the ciliated cells.

As in the mesonephric tubules, the cytoplasm of the ciliated cells stains very lightly and contrasts with the cytoplasm of the secretory cell.

The appearance of the epithelium in the postmenopausal woman has not been studied in any detail. However, in the majority, it is lower but resembles that of the estrogenic phase of the menstrual cycle. Only rarely has cuboidal atrophic-appearing epithelium been encountered.

In a few of the routine sections, we have noted epithelial tubules (Fig. 5) in the broad ligament, obviously not of mesonephric origin, whose epithelium was similar to that of the accompanying oviduct. Findings in four of the serially sectioned broad ligaments established the paramesonephric origin of such tubules.

Fig. 5.—Paramesonephric tubule from the same broad ligament as in Fig. 3. See Fig. 7 for greater magnification and comparison with mesonephric tubule. ×840.

In two of the serials, single tubules were first noted in the substance of the broad ligament at about the junction of mesovarium with ovarian hilum. Both penetrated and ended blindly in the ovarian hilum proper. These tubules extended outward (from the hilum) with few or no convolutions, until both terminated with patent lumina on the surface of the mesovarium adjacent to the "ovarian" fimbria, which happened to be present in both instances. In both specimens, the plane of the section was approximately at right angles to the course of the tubules. One was present for 64 sections or 640 microns. The other was present for 90 sections or 900 microns. Their epithelium had the histologic characteristics of oviduct epithelium and showed the same phase of hormonal response as did the accompanying oviduct.

In a third, a paramesonephric tubule penetrated into the hilar region and terminated blindly near the rete. This tubule differed, however, in that, peripherally, it communicated and was continuous with the lumen of a well-developed accessory oviduct. This particular specimen will be mentioned again when accessory oviducts are considered.

In a fourth specimen, a similar cross-sectioned tubule was noted in the broad ligament at about the junction of mesosalpinx and mesovarium. It was

surrounded on all four sides by mesonephric tubules. Followed in serial section, it abruptly became a complex structure whose long axis was at right angles to the original tubule and extended in the mesosalpinx halfway to the oviduct. This structure was moderately dilated, but insufficiently so to be called a cyst. It was mildly undulating in outline and contained complex "villi" that, except for a moderate amount of "stunting," were identical to those of the oviduct. The epithelium of this structure was similar to that of the accompanying oviduct and was in striking contrast to the adjacent mesonephric tubule epithelium.

This structure can be interpreted only as a blind intraligamentous accessory oviduct and probably had the same origin as the analogous structures to be described later—true accessory oviducts.

In two other serially sectioned specimens, intraligamentous tubules of paramesonephric origin have been encountered. When traced, however, they terminated in intraligamentous cysts.

A final, rather curious, elongated structure should be mentioned. This was in, on, and above the surface of the mesosalpinx of one of the first specimens discussed in this section. Followed in the serial sections, it was found to be above and free from the surface of the broad ligament at each end, with its middle part subserosal. It was lined with oviduct type epithelium throughout and had a well-developed muscular sheath. The smaller free end was moderately dilated. The other appeared bulbous, moderately dilated, and contained many short but typical tubal "villi."

Accessory Oviducts.—Accessory oviducts are usually small structures of variable length and width projecting out from the broad ligament and with open fimbria.

The authors are in somewhat of a quandary as to how to classify accessory oviducts—as a normal or an abnormal finding. Certainly they are too common to be considered pathologic. Their exact incidence is not known. They are inconspicuous structures and are usually not noted by the surgeon, except in the few reported cases where they have been the seat of an ectopic pregnancy. Unfortunately, no record was kept by us as to their relative frequency in the operative specimens.

In the unselected routine pathologic slides examined by us, accessory oviducts were clearly present and with patent fimbria in specimens from eleven patients. In one of these, three separate accessory oviducts were present (Fig. 6) and another had two accessory oviducts. Accessory oviducts are truly miniatures of their normal sisters, with the usual "villi" and similar epithelium, showing the same hormonal response as in the true oviduct.

Accessory oviducts have been present in two of the serially sectioned specimens. In one of these specimens, the pedicle of one accessory oviduct was attached to the broad ligament in the mesovarial region. The pedicle of a second, in this same specimen, was attached to the serosal surface of the oviduct a few millimeters away from the attachment of the mesosalpinx. Surprisingly enough, this accessory oviduct had an accessory of its own, which was attached (to the base of its fimbriae) by a relatively long pedicle. Each of these three accessory oviducts had well-developed fimbriae (although smaller than those of the uterine tube) and patent lumina which penetrated down the stalk for a short distance.

In the second specimen, one accessory oviduct was present. It was attached by a broad pedicle or stalk to the broad ligament directly over the hilar region, with one portion of its circumference near the lateral border of the cortex of the ovary. It had well-developed fimbriae. The lumen of this structure was quite wide until about the area of junction with the hilum. Here it abruptly

narrowed, and the resulting tubule penetrated with an undulating course into the hilum, just short of the rete body, where it abruptly terminated. The penetration of the tubule into the hilum in this specimen has been previously mentioned.

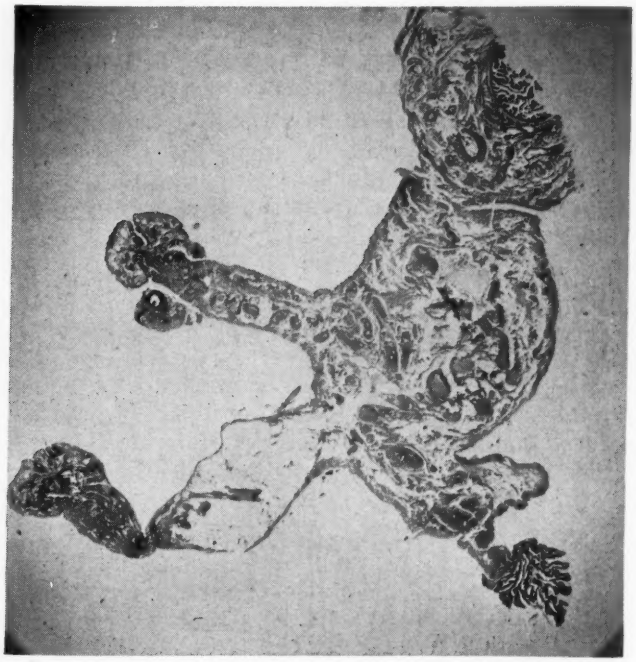

Fig. 6.—Hemi-cross section of oviduct and three accessory oviducts. ×5.

There seems to be but one fairly simple explanation for accessory oviducts, paramesonephric tubules in the broad ligament, and, as will be discussed later, for certain cysts. As previously described under "embryology," the fimbria are formed by a process which starts out in a manner similar to that which results in the formation of the main paramesonephric duct. Multiple miniature paramesonephric invaginations develop in the region surrounding the original duct orifice, grow down, and join the lumen of the latter. If one of these invaginating tubules fails to reach the main duct, it seems likely that it continues partial development as a paramesonephric duct in miniature, and this gives rise to the structures that have been described. The apparent helter-skelter or purposeless distribution of these structures in, on, or under the surface of contiguous structures can also be explained. The main paramesonephric duct grows caudalward and reaches its proper objective by following along the surface (and under the basement membrane) of the already existent mesonephric duct. If the latter fails to develop completely, the development of the duct is correspondingly limited. The paramesonephric duct, therefore, does not have an inherent ability, in itself, to develop in a normal manner. It seems logical to believe that these miniature paramesonephric ducts have this same lack of ability as to direction and extent of growth.

In 1907, Robert Meyer rather severely criticized J. Koch for having reported a tubule derived from the base of the ovarian fimbria and penetrating into the hilum of the ovary as a "Müllerian" duct derivative. Koch's tubule apparently was identical with those of the first two specimens described in this section and was similar to that of the third, except that the latter terminated in the lumen of an accessory oviduct.

To Meyer, it was obvious that these tubules were of mesonephric or even pronephric origin, and certainly not a derivative of the cranial part of the main paramesonephric duct. We agree that they do not originate from the main or primary paramesonephric duct. If the epithelium of the tubule discussed by Koch is similar to that of ours (no histologic details were presented), we are unable to agree with the first part of Meyer's conclusions. The epithelium of these particular tubules was obviously of paramesonephric origin. The junction of the tubule in this region, in the third specimen, with the lumen of a well-developed accessory oviduct is certain evidence that paramesonephric tubules can occur in this region. It seems likely that Koch's specimen and our specimens represent the end results of the unguided wandering of a secondary invagination that was a little too dilatory in its attempt to commune with the primary paramesonephric duct.

Differences Between Mesonephric and Paramesonephric Structures.—As previously noted, the epithelium of mesonephric tubules and that of the oviduct bear some resemblance in that both are made up of ciliated and nonciliated cells. In both, the general distribution and arrangement of the two types of cells are about the same. In both, the ciliated cells stand out in stained sections, due to the almost complete lack of cytoplasmic staining. It is possible, however, to distinguish the two epithelia with a reasonable degree of certainty.

The most obvious difference is that of *nuclear and cell size,* particularly evident in the ciliated cell. In a sense, the mesonephric epithelium gives an impression of being a junior edition of the oviduct epithelium. To confirm our impression, the cell height and nuclear diameter of ciliated cells in 18 specimens have been measured with a micrometer ocular. In eight specimens, measurements were made on ten nuclei and cells in mesonephric tubules and the same in the oviduct, the cells being chosen at random. In ten other specimens, the procedure was similar but only five measurements were made. The average results were practically identical, whether five or ten measurements were made. It is, therefore, presented in the table as the average from the total of 18 patients (Table II). The difference between the nuclei of the two types of epithelium

TABLE II. COMPARISON OF MESONEPHRIC AND PARAMESONEPHRIC CELL AND NUCLEUS SIZE

	OVIDUCT CELL	MESONEPHRIC CELL	DIFFERENCE†	OVIDUCT NUCLEUS	MESONEPHRIC NUCLEUS	DIFFERENCE
Number of cases	18	18		18	18	
Average ± St. error in microns	*18.56* ± 0.96	*12.83* ± 0.47	5.74 ± 1.12	*9.46* ± 0.28	*7.47* ± 0.14	1.99 ± 0.33
t-ratio			5.14			6.04
Probability			<0.01			<0.01
Significance			High			High
Area from diameter*				69.99 square microns	43.88 square microns	

*See text.

†Method: paired comparison, Snedecor, "Statistical Methods," Iowa State College Press, Ames, Iowa, 1946.

is not so striking when presented in terms of diameter (though it is statistically significant). One does not, however, visually or mentally compare nuclear size in terms of diameter but rather in terms of total area. The area of these essentially round structures was therefore calculated from the diameter measurements. The difference is then more apparent. The paramesonephric nuclei have more than half again as large an "area" as the nuclei in the mesonephric tubule epithelium.

The difference in cell height is obvious, as can be seen in the table and in Fig. 7, the paramesonephric ciliated cell being, on the average, approximately 50 per cent greater than the ciliated cell of the mesonephric tubule.

The mesonephric tubule epithelium has a well-defined *basement membrane*, as does its pathologic derivates. (This is also true of the duct and its derivatives.) The oviduct epithelium has no basement membrane.

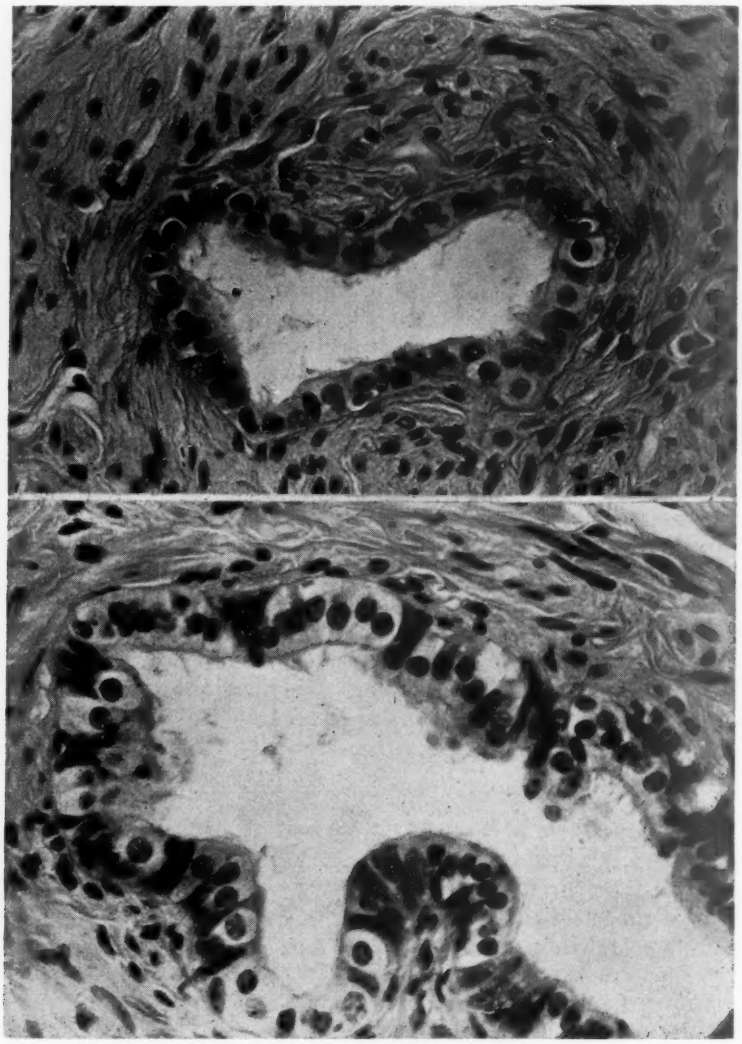

Fig. 7.—Mesonephric and paramesonephric tubules from the same broad ligament and at the same magnification. Note greater size of cells and nuclei in the paramesonephric tubule. ×1995.

Observations on the basement membrane are usually presented in a matter of fact manner—the implication being that this structure is easily recognized and nonconfusable with other structures. This has not been the authors' experience. In sections tangential to the basal epithelial surface, the basement membrane is frequently not visible. In the field being studied, the section must be at right angles to the epithelium before one is justified in stating that a basement membrane is not present. In the ordinary routine hematoxylin and

eosin staining, the basement membrane is a poorly defined structure. In fact, so poorly defined that a continuous smooth-surfaced row of basal epithelial cells with well-defined cell borders may be confused with it. This may be the case at the base of the ciliated cells of paramesonephric epithelium. However, at the base of the secretory cells, the absence of the basement membrane is obvious.

The so-called *villi* are structures characteristic of the oviduct. Few are in reality villi but are transverse sections through folds or plica. Villi are not present in mesonephric tubules and can hardly be confused with the occasional irregularities produced by sections through a sharply angulated bend in the tubule, or with the more minor irregular projections of the epithelium into the tubule lumen, due to rapid and extensive shrinkage of tissue with the use of harsh fixatives.

While *cyclic changes* in the mesonephric tubules during the menstrual cycle have not been studied in detail, it is known that the mesonephric tubule epithelium does not show the characteristic oviduct epithelial changes of the progestational part of the cycle, menses and pregnancy. The projecting nuclei and irregular luminal surface of oviduct epithelium are not characteristic of mesonephric epithelium.

II. Cystic Structures

The authors were in somewhat of a quandary as to exactly how large the dilatation of an epithelial structure had to be before a cyst could be considered present. It was arbitrarily decided that only those would be considered that were macroscopically visible. One hundred and one such cysts were found, including both intraligamentous and pedunculated. An endeavor has been made to determine whether each cyst was of mesonephric or paramesonephric derivation. This determination has been made in 87 of the cysts. In seven specimens, we were unable to determine the origin of the cysts. In seven other specimens, the microscopic preparations were of too poor quality to allow any such determination.

Pedunculated Cysts.—Most authors believe that two types of pedunculated cysts exist. They are differentiated by the site of origin of their pedicle. If it arises on or near the fimbriae, it is called a "hydatid of Morgagni." As a small structure, this is so common as practically to be considered normal. The other is stated to have a pedicle which arises more mesially (closer to the uterus) and from the surface of the broad ligament. The derivation of these hydatids may or may not be the same, depending on what authority is being quoted.

Modern embryologists (Arey, 1942; Hamilton, Boyd and Mossman, 1945; Patten, 1946; Krafka, 1942) and others (Doran, 1884, Schiller, 1946) quite uniformly agree that the hydatid of Morgagni is a paramesonephric derivative. An equal number of authorities, however, believe it to be of mesonephric origin (Pierson, 1916; Quinet, 1944; Watkins, 1933; Craig, Nordlander, 1941; Kieth, 1923). A rather unique view that it has pronephric origin is held by Peel (1944) and by Gilbert and Sheorry (1941). Present-day embryologists are unanimous that, with the exception of the pronephric duct, which doubles in brass and becomes the mesonephric duct, all pronephric structures disappear.

The "hydatid of Morgagni" results from a developmental error in the formation of the fimbriae. One of the secondary invaginations never reaches the main duct. It continues development as one of the previously described accessory oviducts, with the exception that it loses its luminal connection with the primitive peritoneal cavity. Having no orifice, it undergoes cystic dilatation. It, therefore, actually is a hydropic accessory oviduct.

In our own preparations, the early stages in the previously described development of the fimbriae are well demonstrated. In a 22 mm. embryo, epithelial invaginations near the ostium of the main paramesonephric duct are clearly evident, with their down-dipping epithelium reaching but not penetrating the main duct epithelium. In a 24 mm. embryo, these invaginations are more obvious, and some of them communicate with the main duct. This is also the case in a 27 mm. embryo. In the broad ligament of an 80 mm. embryo, a pedunculated accessory paramesonephric duct remnant is attached to the mesosalpinx in the immediate vicinity of the developing fimbriae. A similar structure was found in a 95 mm. embryo. The epithelium in these structures is identical with that of the main paramesonephric duct. They have, however, no orifices. If the embryos had lived, it seems likely that these structures were destined to become hydatids of Morgagni. Interestingly enough, an identical structure was attached to the mesosalpinx of the other side of the 80 mm. embryo. It differed, however, in that the point of attachment of its stalk was overlying the mesonephric tubules (those destined to persist) and was some distance from the paramesonephric duct fimbriae. Its epithelium was identical with that of the paramesonephric duct and did not resemble that of mesonephric origin.

A structure similar to that first described in the 80 mm. embryo has been found in the serially sectioned broad ligament of a near-term fetus. The pedicle was attached in almost immediate contiguity with the base of one of the most lateral fimbria of the oviduct. It had undergone a modern amount of cystic dilatation and its epithelium was well differentiated and identical with that of the oviduct (similar to adult type epithelium).

Twenty-five pedunculated cystic structures were found in the adult material (both routine and serial sections). This group includes both the "hydatids of Morgagni" (pedicle attached at or near the tubal fimbria) and the so-called "Kobelt cysts" (pedicle not attached in the immediate vicinity of the fimbria).

One tissue was omitted from consideration because of its very poor quality. Twenty-two of the remainder were lined with epithelium identical to that of the tube. In almost all instances, sections of the tube were also available. In such cases, the cyst epithelium showed the same characteristics of the various phases of the menstrual cycle as did the tube. In 17 of the 22, "villi" were present. These "villi" had the same basic structure as those of the tube. Other characteristics of paramesonephric epithelium were present.

One of the two remaining pedunculated cystic structures had the usual thin wall composed of fibrous and smooth muscle tissue. It was lined, however, by low cuboidal epithelium with a distinct basement membrane. No cilia were present. This epithelium was identical with that usually found in the mesonephric duct. It seems probable that this was a pedunculated mesonephric duct cyst. This cyst was in the immediate region of the fimbria. It seems likely, therefore, that it represents a development of the most cranial portion of the mesonephric duct remnant.

There remains one pedunculated cyst. We are uncertain of the origin of this structure, since, in some respects, it resembled paramesonephric derivatives, and, in others, mesonephric tubule derivatives.

Even granting that this last specimen was a mesonephric tubule derivative, the final tally on the origin of these pedunculated remains is: paramesonephric 22, mesonephric duct 1, mesonephric tubule 1. This corresponds well with the pedunculated structures seen in the embryos and newborn.

Nonpedunculated Cysts.—The opinions of the various authors as to the derivation of pedunculated cysts were given in the last section. The derivations of those that do not have a true pedicle will be considered here. This group will necessarily include a few small cysts that are sessile.

There is little disagreement as to the nature of the wall of these cysts. They are relatively thin (in contrast with the rare true intraligamentous cystoma, in which the wall of the cyst takes an active part in the growth) and are composed of connective tissue and muscle fibers.

There has been the usual variability in descriptions of the epithelium of these cysts. It has been described as simple cuboidal to flat (Schiller, 1946; Graves, 1929; Novak, 1947), cuboidal to cylindrical (Shaw, 1932; Meigs, 1934), varying in different area from flat to high columnar (Lynch, 1922; Nordlander, 1941; Opocher, 1939), columnar (J. H. Müller, 1942; Forgue and Crousse, 1925). The cells have been described as ciliated (Graves, Shaw, J. H. Müller) or it has been stated that ciliated cells may be found (Doran, Forgue and Crouse, Craig, Nordlander and Lynch). That "papillae" may be found, or that there is a "papillomatous tendency" has been noted (Lynch, Novak, Nordlander, Opocher, Craig, J. H. Müller, Doran, Graves, and Shaw). None of these authors noted the resemblance of these "papillae" to tubal "villi." Such is specifically mentioned, however, by Kossman (1912), and also by Meyer (1912) in describing a "parovarial" cyst, 8 cm. in diameter.

Many ideas have been expressed on the derivation of these cysts. The vast majority of authors, however, believe them to be mesonephric in origin (Cole, 1910; Craig; Crossen, 1946; Coblenz, 1882; Doran; Forgue and Crousse; Nordlander; Quinet; Meigs; and Watkins). Doran clearly differentiates two types, those from the mesonephric duct and those from mesonephric tubules. Gilbert and Sheorry, in 1941, stated that the cysts of any significance are derived from "junctional tubules." These cysts they called "fimbrial cysts"—not because the fimbriae had anything to do with their genesis, but because the fimbriae (and tube) are stretched out over their surface. The junctional tubules," they believe, are derived from pronephric remnants, and, in the embryo, are the progenitors of the rete. Gilbert and Sheorry obtained their embryological data from Keith's Textbook of Embryology (1923). Keith's data on this subject were obtained from an embryologic article devoted to the tortoise, written by Allen, and published in 1905. The fact was ignored that Allen specifically stated that the *rete in mammals was not derived in this manner from pronephric remnants.*

In a textbook published in 1944, Peel essentially repeated the derivations presented by Gilbert and Sheorry, including the derivation of "fimbrial cysts" from "junctional tubules."

Young, in a textbook (1944), and Shaw, in an article (1932), believe that some broad ligament cysts are of mesonephric origin, but both also classify "fimbrial cyst" in a separate group, and both derive them from "ovarian remnants." Shaw goes further and states that these latter do not represent retention cysts (as do those of mesonephric origin) "but true neoplasms, for the epithelium is either cuboidal or columnar, and the incidence of papillomas in the wall absolutely excludes an origin from Wolffian remains." The latter part of this statement is no doubt true.

The most unique idea is that presented by Sutton, in 1886, that "probably many, but not all, broad ligament cysts arise from dilatation of lymphatic channels."

Paramesonephric Origin.—In many articles, the possibility of the paramesonephric derivation of broad ligament cyst is considered briefly and then dismissed as unlikely or impossible. This was done, for example, by Cole, in 1912. In 1914, however, he presented a case report of a broad ligament cyst which was near and under the fimbria (also stretching tube and fimbria over its surface). This particular cyst was a diverticulum of the oviduct, as demonstrated by serial section.

In an article summarizing various ovarian, hilum, and broad ligament abnormalities he had seen, Robert Meyer (1912) noted one 8 cm. broad ligament cyst which he derived from an accessory oviduct. In general, though, he believed broad ligament cysts to be of mesonephric origin. Gilbert and Sheorry also believed that the rare small cysts having epithelium identical with the tube, uterus, or cervix are of paramesonephric origin—accessory oviducts or diverticula therefrom.

Apparently Kossman has stood alone in believing that all broad ligament cysts are of paramesonephric origin. One of his reasons for so claiming, however, was based on a misconception. He believed there was no musculature around mesonephric structures and, since muscle fibers were present in the walls of these cysts, they must be of paramesonephric origin.

In summary, most have believed that broad ligament cysts were of mesonephric origin. A few believe that some may be derived from pronephric remnants. The embryologic data on which these latter claims are based are not very pertinent. The very few remaining investigators were of the opinion that some or all broad ligament cysts may be of paramesonephric origin.

Seventy-six intraligamentous cystic structures, varying in size from 2 mm. to approximately 10 cm., have been found in the present study (in addition to a cystic mesonephric tubule found in the newborn). Six of these have been omitted from consideration because of the poor quality of the tissue. We were unable to be certain whether five other cysts were of mesonephric or paramesonephric origin.

Mesonephric Duct Cyst.—In four of the routine sections, small cysts had the usual relatively thin wall composed of muscle and connective tissue fibers, but their epithelium had a distinct basement membrane and was composed of low cuboidal cells with no cilia. The inner walls were smooth. No villi or papillae were present. The epithelial lining was identical with that usually found in the mesonephric duct. Luckily, a fifth similar cystic structure, whose origin was obvious, was found in a broad ligament that had been serially sectioned. In a single section in the mesosalpinx near the oviduct, there appeared to be multiple small cysts, lined by simple low cuboidal epithelium. Their walls were composed of muscle tissue. The thickness of their walls seemed to vary inversely with the diameter of their lumen. Examination of the serial sections, however, proved that all of the structures were part of a cystically dilated and convoluted mesonephric duct that terminated blindly at the most bulbous end and communicated with mesonephric tubules near the other end (which also ended blindly). These latter tubules were only moderately dilated.

Mesonephric Tubule Cyst.—Thirty-three of the remaining cysts were of mesonephric tubule origin. Their walls had the usual characteristics (Fig. 8). Muscular elements were discernible but were scanty in the larger cysts. This latter fact is also true, incidentally, of the larger cysts of paramesonephric origin. The epithelial cells were plump cuboidal to low columnar, with the previously described arrangement of ciliated and nonciliated cells. Their epithelium was similar in all respects to that of the mesonephric tubules.

We had expected the epithelium to be flattened in the larger specimens, due to intracystic pressure, and it is true that, in some specimens, areas could be found with the epithelium flattened and almost squamous-like. However, in every specimen (including those both of mesonephric tubule and paramesonephric origin), most of the epithelium was healthy and showed no appreciable evidence of flattening. The only exceptions to this occurred in cysts in which all of the tissues in the slide were shriveled or shrunken. Such tissues, as previously mentioned, are not included in this study.

In this regard, it must be re-emphasized that the details presented in this study will be found only in tissues that have been treated with respect and care. Few of them will be discernible in the routine preparations of the pathology departments of some hospitals, at least. Delays of several hours before fixation, use of harsh fixatives, rushing tissues through an autotechnicon, and careless technical work combine to produce tissues that are very poor shadows of their former selves. Such factors, no doubt, contribute to some of the misinformation on the subject under discussion.

The histologic details that served as diagnostic points, to differentiate these cysts from those of paramesonephric origin, will be presented in the next section. The diagnostic value of location, as well as the presence of mesonephric tubules in the wall of, or adjacent to, the cyst, will also be considered there.

Fig. 8.—Wall of intraligamentous cyst of mesonephric tubule origin. Note resemblance of epithelium to that of mesonephric tubule in Figs. 3 and 7. ×1995.

Mesonephric tubule cysts of varying size were found in six of the serially sectioned broad ligaments. The smallest ones were completely included in the sections; only part of the wall was included in the others.

One of these small cysts occurred as a spherical cystic structure, fairly close to the uterine tube. It was near, but not in continuity or even contiguity with, mesonephric tubules with whose epithelium it was identical. This cyst occurred, we believe, as a result of the cystic dilatation of an isolated remnant of a mesonephric tubule. Such isolated tubules, in this and in other locations, have been found in our serial sections.

Another was first noted as a single cystic structure in the immediate vicinity of, and partially surrounded by, rete cords and rete tubules. There was no luminal continuity, however, between this structure and the rete. When traced through successive slides, it was seen to be a cystically dilated and highly convoluted mesonephric tubule that progressed toward, but did not reach, the mesonephric duct.

Cysts of Paramesonephric Origin.—The remaining 27 intraligamentous cysts were considered to be of paramesonephric origin. This figure does not include the five intraligamentous cysts of whose origin (mesonephric tubule or paramesonephric) we could not be certain.

The wall of these paramesonephric cysts did not differ from those of mesonephric tubule origin, as described in the previous section. Also similar to mesonephric tubule cysts, occasionally areas of low flattened epithelium were found.

"Villi" were found in 22 out of the 27 specimens. They varied in size, or rather, in apparent length in the various specimens, from relatively minute (but

definite) isolated structures to elongated, fairly complex structures with subbranches. In general, the number of villi, the ease with which they were found, and their degree of development seemed to vary inversely with the size of the cyst.

The epithelium of these cysts was identical with the previously described oviduct epithelium (Figs. 9, 10). Sections of the uterine tube were available with most of these specimens. The cyst epithelium showed the same response to cyclic changes in the sex hormones as did the tubal epithelium.

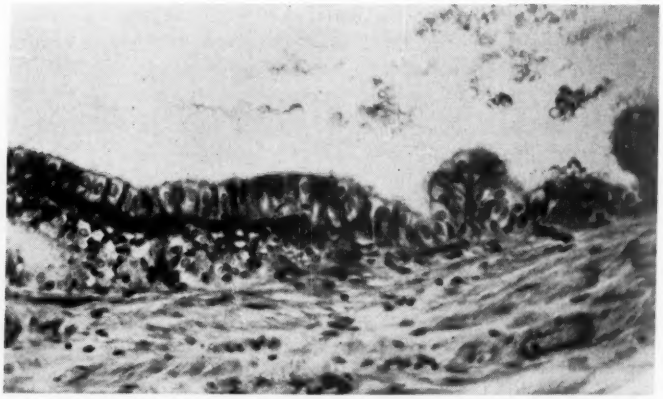

Fig. 9.—Wall of intraligamentous cyst of paramesonephric origin from the same broad ligament as Fig. 4. Note similarity of epithelium. ×840.

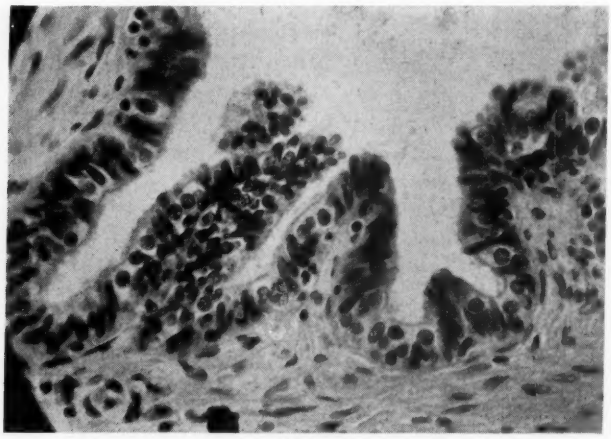

Fig. 10.—Wall of intraligamentous paramesonephric cyst showing progestational response. ×1425.

Paramesonephric cysts were present in four of the serially sectioned broad ligaments. One of these was first noted as an isolated spherical structure, fairly close to, and between, the rete and a group of mesonephric tubules. Several small villi were present, and the epithelium was in the progestational phase of the cycle, as was that of the uterine tube (a corpus luteum in the late vascular phase was found in the other ovary). In subsequent sections, it was determined that this solitary structure was the more bulbous end of a dilated and gently

undulating paramesonephric tubule. In another serial, a similar structure was found in the mesosalpinx, adjacent, but external, to the uterine tube musculature.

Differences Between Cysts of Mesonephric and Paramesonephric Origin.— In most instances the difference in *cell and nuclear size,* particularly in the ciliated cells, is fairly obvious. These differences are similar to those which have already been described in the sections on normal oviduct and mesonephric epithelium. In deciding whether a cyst is of mesonephric or paramesonephric origin, comparison of the epithelium of the cyst with that of the oviduct in regard to nuclear and cell size is very helpful, as is comparison with the epithelium of near-by mesonephric tubules.

The epithelium of cysts of paramesonephric origin shows the same response to sex hormones as does the tubal epithelium. This in itself is of utmost value in differentiating the two types of cysts. If the tubal epithelium shows typical progestational, menstrual, or pregnancy changes, paramesonephric cyst epithelium will show the same change. Mesonephric cyst epithelium shows no such change. Instead, the relatively smooth luminal surface of the epithelium is maintained, and nonciliated cells are approximately the same height as the ciliated cells. In fact, the presence of a tube for comparison is not necessary, if the cyst epithelium shows typical progestational, menstrual, or pregnancy changes, because it is automatically paramesonephric since mesonephric epithelium shows no such change.

In estrogenically stimulated epithelium of paramesonephric origin, ciliated and secretory cells are of approximately the same height. The luminal surface, therefore, no longer has the "uniform irregularity." However, there is, in this phase, definite increase in cell and nuclear size (Cowdry's "Special Cytology"). This exaggerates the difference in this regard between paramesonephric and mesonephric epithelium, and thus actually aids in differentiation between the epithelia of cysts of mesonephric or paramesonephric origin.

The villi in these cysts have almost uniformly been termed papillae or papillomatous processes. Properly used, papillae are projecting nipplelike structures. Actually, these processes are typical of oviduct folds or villi, both as to epithelium and stroma. Their presence is diagnostic of a paramesonephric origin of the structure concerned. No such structures have been observed in normal mesonephric tubules or duct, nor in cysts whose origin can be definitely traced to mesonephric tubules, in the serial sections. The only vague possibility of confusion may occur in routine sections, where apparent intraluminal projections may be formed in acutely angulated, cystically dilated, convoluted mesonephric tubules.

Absence of *basement membrane* in oviduct epithelium (at least in the ampullary and fimbrial portions), paramesonephric tubule epithelium, and paramesonephric tubule cyst epithelium was noted relatively late in this study. The absence of a basement membrane in uterine tube epithelium is ignored in textbooks of histology, and even in the cytological bible, Cowdry's "Special Cytology." The presence of a basement membrane can sometimes be noted with a high dry in hematoxylin and eosin routine preparations. Its presence or absence can be determined only with consistent accuracy, however, under an oil immersion lense, and preferably with iron hematoxylin stains.

In the tissues examined for this detail, and under these conditions, a basement membrane was present in cysts which by all other criteria were of mesonephric tubule origin. It was not present in those of paramesonephric origin examined under similar conditions.

Various authorities have stressed the location of the cyst as of extreme importance in determining the origin of the cyst. For example, the position of a so-called "fimbrial cyst" (Gilbert and Sheorry, Peel, Shaw), situated in

the lateral portion of the broad ligament with the fimbria and tube stretched over its surface, necessarily indicates its pronephric origin. Actually, any cyst of any origin (excluding the extremely rare cyst originating mesial to the ovarian artery) of "clinical" size necessarily causes the tube and fimbria to be stretched out over the surface.

The available space in the broad ligament being what it is, it seems logical to us that any and all cysts over a few centimeters in diameter would fill this space and thus be indistinguishable on this particular basis. Certainly, in the material available to us, intraligamentary cysts of mesonephric tubule or paramesonephric origin showed no evidence of being distinguishable on this basis. Since the mesonephric duct normally courses closer to the tube than the mesonephric tubules, one would expect the smaller cysts of this origin to be very close to the oviduct. As a matter of actual fact they were, but similarly sized cysts of mesonephric tubule or paramesonephric origin were also found in different specimens in the same area.

Analogously, one might think it quite logical that small cysts located near the rete would of necessity be mesonephric tubule in origin rather than paramesonephric. As a generality, this might usually be true, but as a necessary criterion of the origin of a small cyst at hand, it has no value. As previously stated, paramesonephric cysts were found in the serials (and also in routine specimens) developing relatively close to the rete.

It, therefore, seemed to us that the precise location within the broad ligament of a specific cyst is not necessarily indicative of its origin.

The presence of mesonephric tubules in or near the cyst wall is indicative, according to some authors, of its mesonephric origin. We have no doubt that one is more likely to find mesonephric tubules in or near the wall of a mesonephric cyst than of a paramesonephric cyst. However, mesonephric tubules have been found in or near the wall of some paramesonephric cysts. It, therefore, seems doubtful that their presence could be used as the criterion for diagnosis of a specific cyst.

A simple, logical histogenic classification of broad ligament retention cysts is as follows:

I. Mesonephric origin
  A. Mesonephric duct cyst
    1. Intraligamentous
    2. Pedunculated
  B. Mesonephric tubule cyst
    1. Intraligamentous
    2. Pedunculated
II. Paramesonephric origin
  A. Paramesonephric cyst
    1. Intraligamentous
    2. Pedunculated

Conclusions

1. Much of the existing confusion in classifying normal and cystic structures of the broad ligament can be eliminated by discarding terms based on proper names and using those having histogenic significance.

2. Certain well-developed structures derived from the embryonic mesonephros are present in the adult broad ligament, and can easily be demonstrated in properly fixed, properly sectioned, and properly prepared tissues.

3. Mesonephric ducts, mesonephric tubules, and paramesonephric structures, as well as their respective cystic derivatives, have an individual and a characteristic histologic appearance; each can be identified with ease.

4. It is possible to classify most broad ligament cysts on the basis of the character of their lining epithelium; but it is impossible to classify them accurately on the basis of their location in the ligament.

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Discussion

DR. ROBERT T. FRANK.—I was brought up in the old-fashioned way and thought in terms of the Wolffian duct, the Müllerian duct, Gartner's duct, epoophoron and paraophoron, and my reaction to this paper was at first one of revolt at a new nomenclature. However, when I saw the huge material and the tremendous amount of work and research that he and his co-workers had expended on this subject, I was willing to forgive them and went to work to brush up my forgotten embryologic knowledge. I was amply repaid, because he has clarified a very mixed-up and little-understood subject in a surprising fashion. I warn him, from personal experience, that it is very difficult to change a well-established nomenclature. However his method of classification really clarifies the subject. I used to shy away from it and waded through I do not know how many of Robert Meyer's pamphlets telling of these things and got very little knowledge from them, but after having read this paper and studied it carefully, I have gotten considerable satisfaction from it. Perhaps to help you understand some of it, I have a few slides which I want to show and which will give you an idea of how I worked so as to get used to this new nomenclature.

Dr. Gardner has introduced order into this field, but it probably is of greater interest to the pathologic than to the clinical branch of gynecology. From the clinician's point of view, you get cystic structures in the broad ligament. The smaller ones are usually an incidental find; the larger ones are felt by the clinician in his pelvic examination and sometimes induce his exploration of the abdomen for intraligamentous tumors and sometimes non-intraligamentous ones, which are pedunculated. He has the satisfaction of knowing, from what Dr. Gardner and other observers have found, that malignancy is practically unknown in these tumors. I believe that Robert Meyer described two adenocarcinomas, arising in what he felt were the lower ends of the mesonephric duct, which he called Gartner's duct. With that exception, I don't know of any malignancy arising from this source. If large, there is serious difficulty in extirpation because some of them hug the ureter.

I recall a striking case which caused me a great deal of trouble—a woman came to me in the later months of pregnancy with tremendous varicosities of the vulva. She had a bulging cystic mass which practically closed off the vagina and bulged into the buttocks. At that time I could not examine her much further and delivered her by cesarean section (this is many years ago). After full involution, the varicosities had greatly diminished, but she had a string of large cysts which started in the buttocks, went along the vagina, went through into the broad ligament and the uppermost one was almost pedunculated in the broad ligament, causing extreme difficulty of extirpation, which had to be done both from above and below.

I will say that I leave here with the feeling that in the future I will be less confused when I see any of these structures under the microscope.

DR. ANDREW A. MARCHETTI.—I have little to add to Dr. Frank's discussion.

One point which interested me was the fact Dr. Frank brought out, namely, that the structures of the paramesonephric duct, or the Müllerian duct, reacted to the estrogenic and the corpus luteum hormone. This response to hormones is a manifestation of the function to which the derivative of the paramesophrenic duct, the oviduct, must adapt itself in the reproductive cycle.

DR. BENJAMIN P. WATSON.—I have always been in favor of discarding proper names for structures and everything else. It is the most confusing thing in medical, surgical, and gynecologic literature. People speak to me about So-and-So's operation and I have to ask, "What operation is that?"

Let us discard these proper names and give them proper embryologic, histologic or pathologic descriptions.

DR. HOWARD C. TAYLOR, JR.—The first question I would like to ask is about this new nomenclature. I agree that this is an important advance from the complicated terminology involving the use of a lot of personal names. I wonder why Dr. Gardner, when he

was producing this revolutionary nomenclature, did not go further and avoid the confusion between "mesonephric" and "paramesonephric." I do not see why the duct which eventually forms the uterus and tube should be named in relationship to its embryonic position, next to the duct of the mesonephros. Why should it not be named the "premesonephric" duct? So, having thought of this subject for the last forty-five minutes since Dr. Gardner brought it up, I raise the question why, when he was making changes in nomenclature, he did not devise a terminology which would be relatively easy for the practical person to follow and remember.

The second question I would like to raise is whether he may be substituting simply one piece of dogma for another. He has attacked the designation of certain structures in the broad ligament as of mesonephric origin, or of paramesonephric origin, on the basis of their general topographic relationship in the broad ligament, to the oviduct or other structures. On the other hand, he is making the assumption that, because certain histologic structures in the broad ligament possess a certain physiologic capacity to respond to certain hormones, they may be regarded as derived from certain embryonic structures which he has named.

Many of the structures in the female pelvis are subject to constant morphologic change. In the pelvic peritoneum you may get cilia and endometrial-like tissues, even mucus-producing cells. These changes are an indication of the transformation, regardless of origin, which may take place in this region. Therefore I would like to be certain that structures in the broad ligament with a low columnar epithelium and with definite basement membranes are derived from embryonic mesonephric structures, and those which have less definitely basal membranes, and those which tend to high columnar epithelium are, as examples, derived from paramesonephric or premesonephric epithelium. I would like to be reassured that Dr. Gardner is not substituting one assumption for another by discarding identification through topography and accepting an equally uncertain identification through histology.

DR. CLAUDE E. HEATON.—I, for one, am loathe to part with all eponymous nomenclature. Kaspar Wolff was one of the founders of modern gynecology. Surely, he deserves to be remembered, and it would seem easier to remember the term Wolffian body than ren primordalis. There are those who would rename the tendon of Achilles. Many of us would agree with the anatomist, F. Wood Jones, that a subject which has lost its tradition is likely to lose its soul. Those interested in nomenclature should consult Jessie Dobson's *Anatomical Eponyms*, published in 1946.

DR. GARDNER (Closing).—To Dr. Taylor I can only say that one of our endeavors has been to introduce to clinicians that terminology which is accepted by authorities in embryology. Furthermore, our studies started with the careful examination of serial sections from embryos; next, we studied broad ligament tissues from newborn infants; and finally, after studying many specimens from adults, we came to the conclusion that the structures which were found in the embryos were the structures that are present in adults.

We are convinced that we are not introducing a new dogma that is without foundation. We believe that these broad ligament structures have not resulted from some type of metaplasia, or neoformation, but are the structures present in the embryo which are carried over into adult life.

THE POSSIBLE SIGNIFICANCE OF ARTERIAL VISUALIZATION IN THE DIAGNOSIS OF PLACENTA PREVIA*

A Preliminary Report

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(From the Department of Gynecology and Obstetrics, St. Louis University School of Medicine)

ARTERIOGRAPHY is a method by which the outline of arteries may be seen on x-ray plates following the injection of radiopaque substance. This has been carried out on almost every organ and region of the body, including the arterial circulation of the brain, the chambers of the heart, the extremities and the abdominal organs. Probably the greatest contribution in the field of aortography was made by the urologists, following the reported work of Dos Santos. Aortograms have been reported in this country by Nelson, Doss, Vitt and Melick. The number of cases reported in literature is well over 3,000 and, so far, no fatality has been reported which could be attributed directly to this procedure.

The first report of aortograms on pregnant women appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, in April, 1935. In an article entitled "Abdominal Circulation During Late Pregnancy as Seen by Aortograms" the authors, W. E. Coutts et al., of Santiago, Chili, described this procedure on twelve women in the eighth month of pregnancy. This was performed under spinal anesthesia. The authors reported the death of one patient from meningeal hemorrhage following lumbar puncture. The authors made three valuable contributions. First, in the article is the statement "In Figs. 1 and 3 we can observe the injection of some placental sinuses, and in Fig. 3 certain vascular structures appear, which apparently do not correspond to the maternal circulation, and which we, therefore, believe to belong to the fetal circulation." Second, the authors showed the deviation of the aorta to the left in pregnancy. Third, they observed no ill effects on the mother or fetus immediately following the aortograms. However, there was no report as to the eventual outcome of the pregnancies.

It was conceived that by delaying the time of exposure, following the injection of opaque solution into the aorta, the maternal circulation over the placental site might be visualized by x-ray. This procedure was carried out on 68 women in the later stages of pregnancy.

Preoperative Procedures

The patients selected for this series were obtained from the Clinic of Firmin Desloge Hospital and private practice. Their ages varied from 20 to 35 years. Parity was not considered later, but, in the early stages of the investigation,

*Read at a regular meeting of the St. Louis Gynecological Society, Dec. 11, 1947.

only primiparas were selected. Preoperative routine consisted in a routine workup, including a P.S.P. test and N.P.N. determination. Particular emphasis was placed upon the kidney function of the patients since the opaque solutions, both sodium iodide and Diodrast are excreted by the kidney. All patients were rejected in whom the results of these tests were not within normal limits. The fetal heart tones were checked at intervals and recorded. When it was determined that the patient was a suitable candidate for investigation, she was tested for sensitivity.

Sensitivity Tests

Both sodium iodide, 80 per cent, and Diodrast, 70 per cent, were used in this series. The 40 per cent solution of Diodrast was used for sensitivity tests. An intradermal injection was made, and, if this produced no reaction, 1.5 c.c. were injected intravenously. If no changes, such as headache, swelling of the tongue or nasopharynx were observed after one hour, the patient was considered not sensitive to Diodrast. The patient received 1.5 c.c. of the 80 per cent solution of Na Iodide intravenously, and the temperature, pulse, and blood pressure were recorded at 15 minute intervals for one hour. If no marked changes were observed, it was considered safe to inject the amount necessary for arterial visualization. Transient pain in the arm, shoulder, and chest, on the side of the injection, was a frequent observation and was not considered a contraindication. Symptoms of acute iodism were not encountered in this series; however, two patients were rejected because of a positive intradermal reaction to Diodrast. The patients received an enema three or four hours before the procedure began, and food and fluids were withheld for six hours. Preoperative medication was 1/150 grain of atropine sulfate, given thirty minutes before administration of anesthesia.

Special Apparatus

The pressure apparatus was made by the W. and H. Company for the administration of Pentothal sodium. A 50 c.c. syringe and high pressure tubing at least 20 to 24 inches in length, with a firmly attached glass bulb, with all connections firmly tied onto Luer-Loks, were used to inject the solution through an 18 gauge needle about 15 cm. in length. The arm, as seen in Fig. 1, was attached to the pressure apparatus for convenience, and proved satisfactory.

Operation

The puncture of the aorta was performed on the x-ray table. Lateral, oblique, and prone positions were investigated, and the most satisfactory was found to be the prone position. The patient's thighs and chest were comfortably supported by pillow padding. The puncture was made from the left side. Pentothal sodium intravenously was chosen for anesthesia because of its ease and simplicity of administration, and it proved to be very satisfactory. Most cases required less than 0.5 Gm. for the entire operation, although one patient received 2 Gm. without ill effect.

The actual puncture of the aorta is a simple procedure. While the area over the site of the puncture is prepared for aseptic technique, pressure cuffs are applied to each thigh as high as possible. This prevents a loss of the opaque solution to the lower extremities. Pressure of about 200 mm. Hg is necessary to constrict the circulation. When the patient is well anesthetized, the pressure cuffs are expanded. A needle with stylet is inserted into the spinal muscles three fingerbreadths from the spinous processes at the level of the lower border of the twelfth rib. The needle is directed superiorly and slightly medially. When contact with the body of the vertebrae is made, the needle is withdrawn slightly,

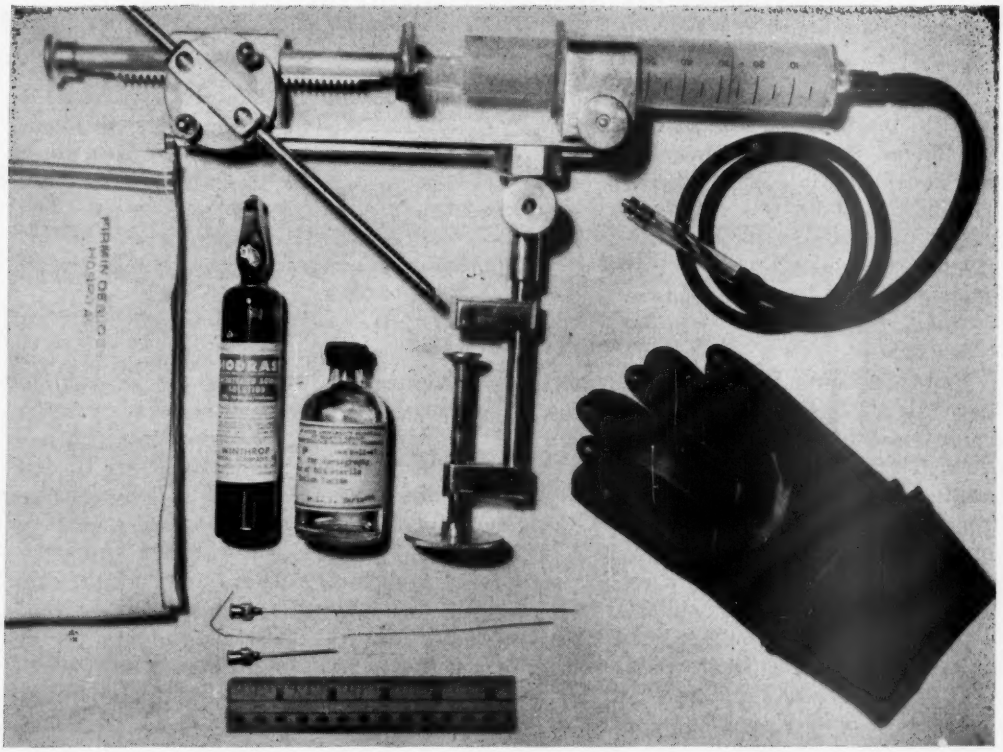

Fig. 1.—This illustrates the special equipment necessary for aortal injection. The pressure apparatus was made by the W. & H. Company for the injection of Pentothal. The needle is 18 gauge and 15 cm. in length.

Fig. 2.—Illustration of the position of the patient found most satisfactory, with the pressure apparatus in position. The search plate should be taken before the administration of Pentothal. The preoperative setup should be complete before aortic puncture is made.

the stylet removed, and then directed slightly to the left or laterally. The actual puncture of the aorta can be felt and is evidenced by a flow of bright red blood. Actual pulsation of the flow is not always visible. It can be seen, however, within the glass bulb, when the pressure apparatus is attached. When the puncture has been made, the needle should be inserted further to a depth of 0,5 to 1 cm. When the operator is satisfied that the point of the needle is well

Fig. 34.—Search film using soft tissue technique.

within the lumen of the aorta, the pressure apparatus is attached, and 10 c.c. of sodium iodide (80 per cent) or at least 18 c.c. of Diodrast (70 per cent) are injected into the aorta over a period of about five seconds. Sodium iodide, when injected more rapidly, causes considerable irritation of the arterial bed, and a contraction of the uterus is observed frequently. Diodrast, unless injected at this rate, is not present in sufficient concentration to produce opacity in the x-ray plates. The first x-ray exposure is made as the injection is completed. A second exposure is made within an additional seven seconds. A longer delay usually produces unsatisfactory results.

X-Ray Technique

This procedure should be adaptable to any ordinary hospital x-ray equipment. The majority of satisfactory plates were obtained with a setting of 75 kilovolts, 200 milliaperes, at 0.5 second with a high speed Bucky grid. A rotating anode tube was employed, and is considered desirable. The best plates by far were obtained with sodium iodide as the injected solution. Diodrast, while considerably less irritating, requires a greater concentration, and the outline of the vessels is not clear. There is need for a more satisfactory injectable opaque solution.

Fig. 3*B*.—Aortogram taken as the injection is completed. The maternal arterial circulation is outlined, and there is the characteristic mottling about the vessels which is probably the maternal sinuses of the placenta.

Postoperative Treatment

The anesthetic is withdrawn as soon as the injection is completed. After the x-ray plates have been exposed, the patient is immediately transferred to a cart, and the condition of the uterine musculature is observed, and the heart tones are checked at regular intervals. When the condition of the patient is considered satisfactory and the heart tones are normal, the patient is transferred to the division, and 1,000 c.c. of normal saline and 500 mg. of vitamin

C are given intravenously as soon as possible, in order to increase the rapidity of the excretion of the opaque solution. 100 mg. of Demerol has proved satisfactory to relieve pain and restlessness which may be present.

Complications

Extravasation of the injected solution was the most important complication encountered thus far. When this occurs, the solution has been injected into the adventitial tissue about the aorta, as shown by x-ray. Since the puncture

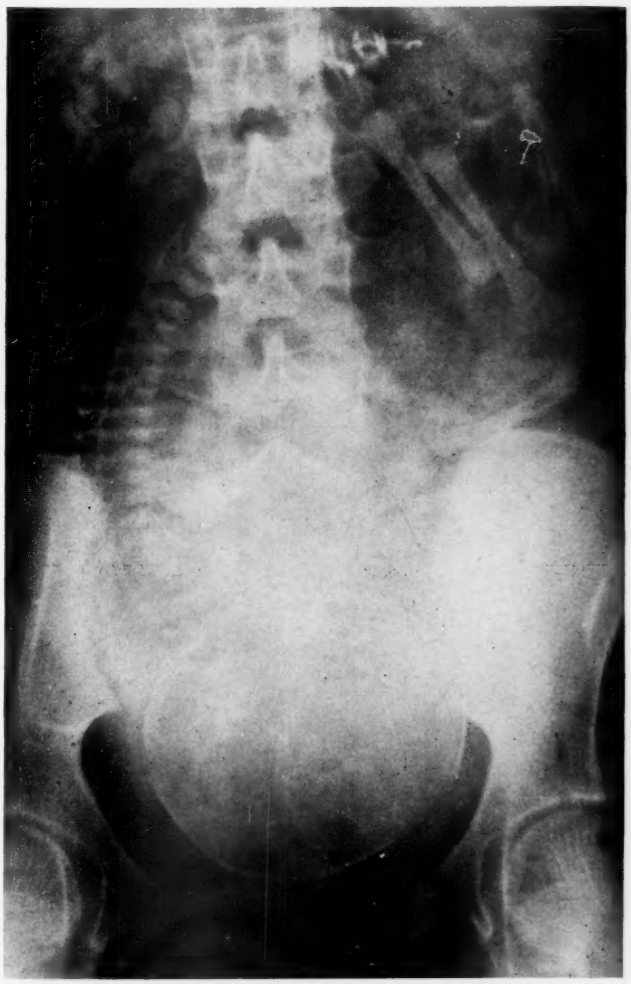

Fig. 3*C*.—Delayed exposure (10 plus seconds), showing the outline of the sinuses. No photographs in this article have been retouched.

is on the posteriolateral aspect of the aorta, it is logical that the extravasated solution will be retroperitoneal in every instance. Thirteen such accidents occurred in this series and, except for pain in the lumbar region for twenty-four to forty-eight hours, an elevation of temperature to 100° F. in two cases, for twenty-four hours, no ill effects were observed. Immediate evidence of extravasation is shown in the patient by hyperventilation and a catchy type of stertorous breathing which subsides after a few minutes. This is probably a result of irritation. The discomfort was controlled by 100 mg. of Demerol given

whenever necessary. X-ray plates taken at intervals showed the complete absorption of the solution in from twelve to seventeen hours. All patients in whom the procedure was successful were allowed to leave the hospital after

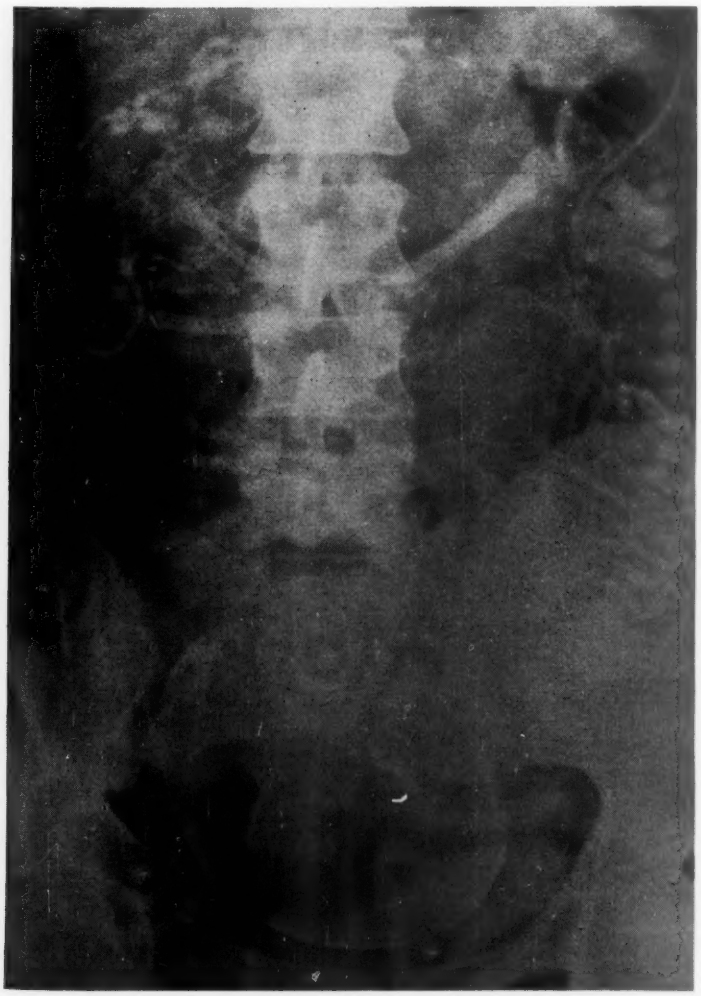

Fig. 4.—Characteristic appearance of the normally located placenta, showing the mottling about the maternal arteries.

eighteen hours. Those in which extravasation occurred were allowed to leave when the pain subsided, usually within forty-eight hours. Injection of a specific vessel, such as the left renal artery, celiac axis, hepatic artery, and the splenic artery, occurred during this investigation without ill effect. The first case attempted received the entire amount of the solution (15 c.c. 80 per cent sodium iodide) into the left renal artery, and, after four months of careful and complete observation, no pathological changes have been observed.

Postoperative Observations

Particular emphasis was placed on the observation of the behavior of the uterus after the injection. Sodium iodide is irritating to the intima of the arteries when the concentration is high. The first few cases in this series received

15 c.c. of this solution at a rapid rate, and, in these, a mild to moderate tetanic contraction of the uterus was observed, which began about one and one-half minutes after the injection and continued for five to eight minutes. During this time the fetal heart rate was counted as low as 76 per minute, rapidly returning to a normal rate, or above, shortly thereafter. This fall in rate in one case was considered physiological, as a result of the contraction of the uterus, rather than a reaction from the effect of the sodium iodide directly upon the fetus. Later,

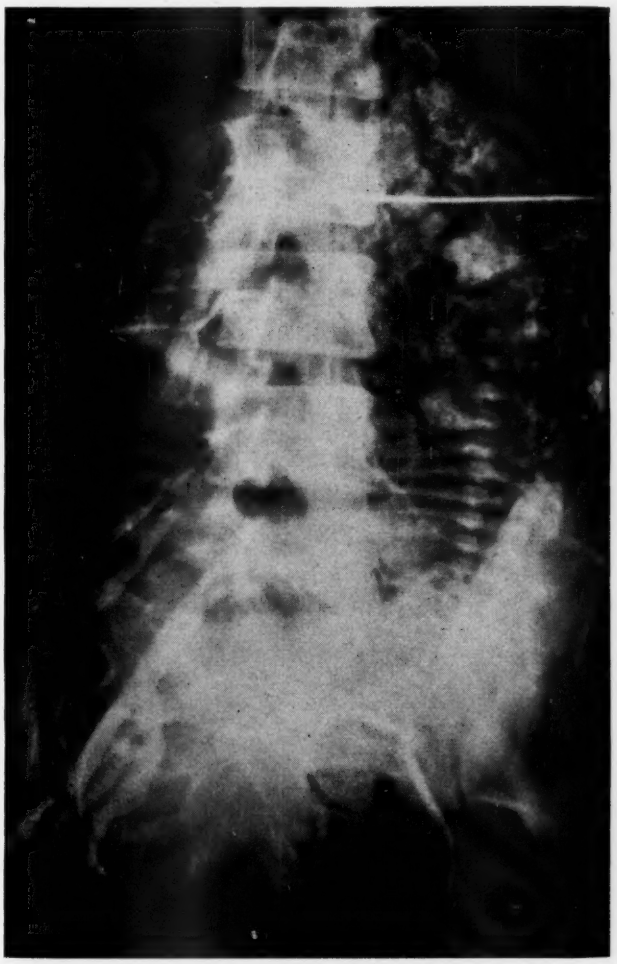

Fig. 5.—This illustrates the implantation of the placenta in the region of the fundus and to the right.

when the amount of sodium iodide was decreased to 10 c.c. and the time of injection increased, thereby decreasing the concentration in the aorta, the contraction was slight and short in duration, and no marked change in the fetal heart rate was observed. Diodrast, when used, produced no evidence of irritation, and, therefore, no changes in the tonus of the uterus or changes in fetal heart rate were observed.

Early in the investigation, only patients at or near term were chosen. Many of these began labor immediately or shortly after the aortic puncture. However, as cases were selected with pregnancies of shorter duration, no incident of premature labor was encountered. All women in this series delivered

without mishap, and all babies were living and apparently unaffected. Mothers and infants were released from the hospital after the usual routine lying-in period.

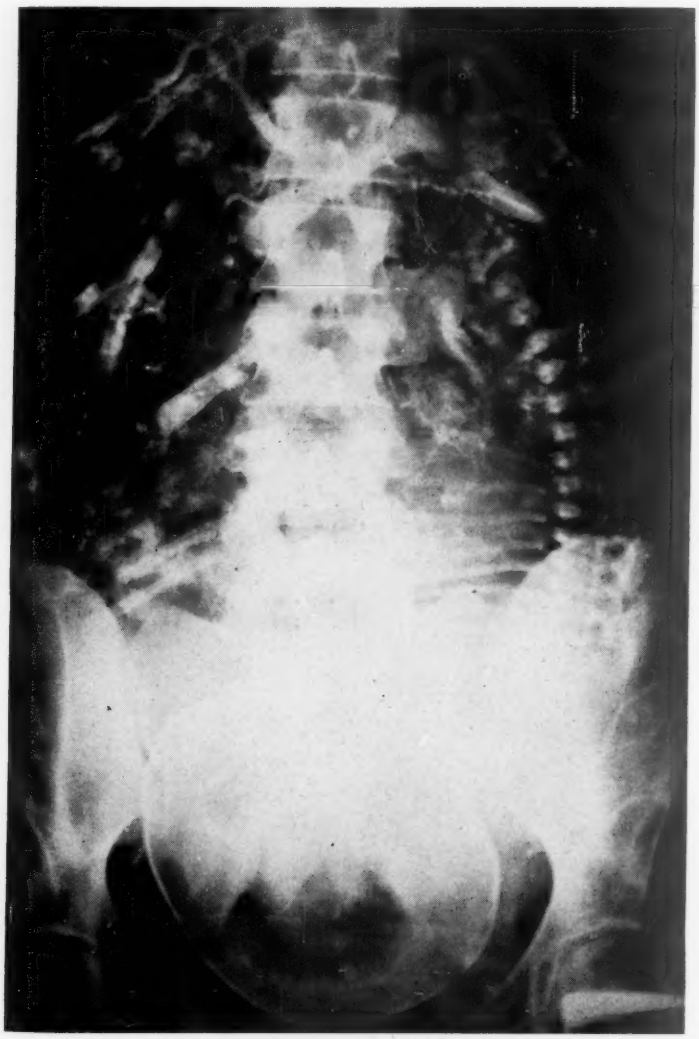

Fig. 6.—The placenta is implanted in the region of the fundus and to the left.

Starch tests on the placentas were negative for iodide, and microscopic examination failed to produce evidence of damage to the chorionic villi. Whenever possible, the location of the placenta was determined manually after delivery, and, in each instance, when done, the location corresponded to that seen in the x-ray plates. One case of placenta previa came to cesarean section, and the location of the placenta was verified at the time of operation.

Discussion

There is need for a positive means of localizing the placenta. Bleeding during pregnancy is difficult to evaluate, and the decision for treatment is often made, necessarily, with no assurance of its correctness. This investigation was

devised, with the hope that it would offer a safe method as a diagnostic adjunct. When successful, it leaves no doubt as to the actual position of the placenta, and it eliminates the necessity for a vaginal examination.

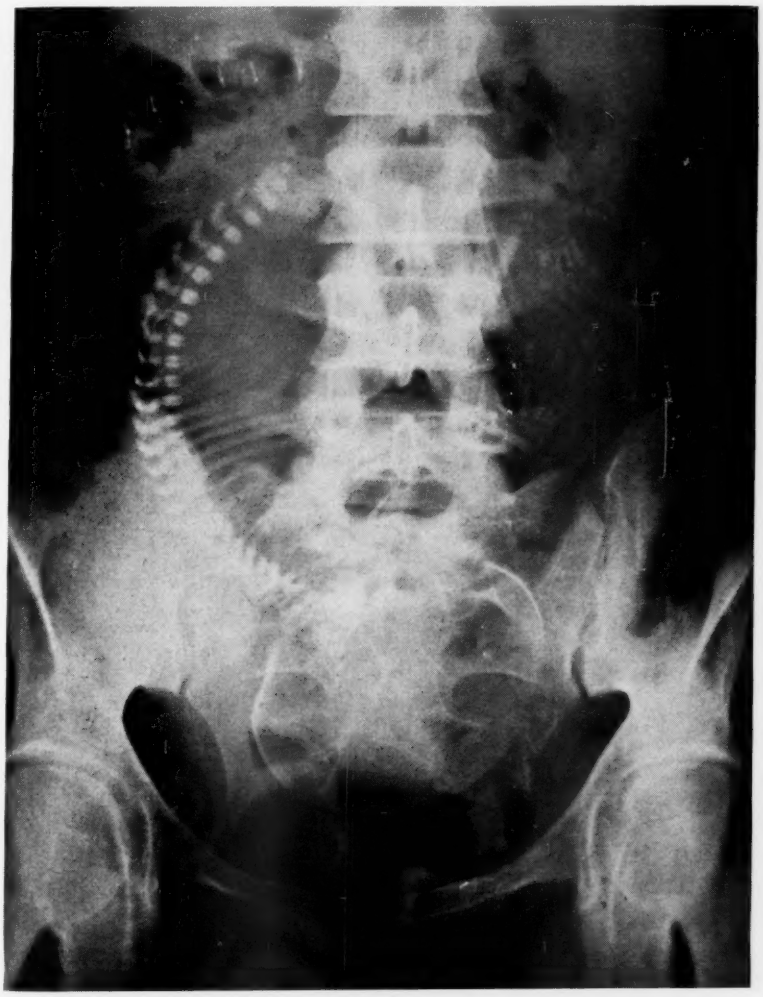

Fig. 7A.—Search film taken of a patient at the twenty-eighth week of pregnancy. She entered the hospital because of a moderately severe hemorrhage.

Two cases of bleeding were encountered, one at the thirty-first week of pregnancy and the other at the twenty-eighth week of pregnancy. Aortograms were performed on these patients with no ill effects. There was no bleeding produced within 48 hours following the injection. The first patient was allowed to go to the thirty-seventh week of pregnancy before cesarean section was performed. The baby was lying in a transverse presentation and the location of the placenta was verified. The other case was allowed to progress to the thirty-eighth week of pregnancy and cesarean section was performed with successful outcome.

In both instances there was a question as to the cause of bleeding. If the bleeding had been produced by the separation of a low-lying placenta, the at-

tending danger to the mother and baby would be less than that bleeding which might be produced by an abruptio placentae. Since the hemorrhage, in both instances, was profuse and sudden in onset, gradually subsiding, the aortograms proved very useful when making a decision for treatment. In such cases, when consideration must be given to the viability of the baby, and a choice between

Fig. 7*B*.—Aortogram on patient (Fig. 7*A*) showing outline of maternal arteries over the lower segment. The characteristic mottling of the maternal sinuses is making its appearance below the fetal head. This is a case of central placenta previa, diagnosed at operation.

conservative and radical treatment is to be made, this should prove useful. In cases of profuse, unrelenting hemorrhage, when treatment must be instituted, it is certainly of no value. It becomes a question, at this point, whether the risks involved in aortography are worth while, in comparison with the hazards of watchful expectancy. While the results to this point have been satisfactory, and, even in the face of failure and extravasation, the patients do not seem to

have been harmed, I personally feel that the series is not large enough to come to a definite conclusion. The investigation will continue, and it is hoped that interest will be shown by others, in order to help improve the technique and to find a better injectable radiopaque solution. It appears evident that the procedure is sound, and the failures have been the result of errors in technique rather than a lack of fundamental soundness.

Fig. 7*C*.—This plate was exposed seven seconds after Fig. 7*B*, showing the solution remaining in the sinuses. The renal circulation is well outlined.

Summary

1. Aortograms were performed on 68 women during the later stages of pregnancy without serious complications.

2. When the procedure was successful, by delaying the time of the x-ray exposure, an outline of the maternal circulation over the placental site was visualized.

3. Two cases of placenta previa were encountered in this series.

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THE CHARACTERISTICS IN HYSTEROSALPINGOGRAMS IN TUBERCULOUS SALPINGITIS AND ENDOMETRITIS*

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I HAVE chosen the above topic for discussion, from the findings which are derived from the clinical material from the Woman's Hospital, Shanghai, China, since its opening on Jan. 17, 1935, to Jan. 9, 1947. They are not something new, nor do they represent experimental work, but they have appeared in our clinical routine to be of such a particularly unique and persistently constant picture that it is deemed worth while to put them on record.

In the literature, twenty-four contributions on hysterosalpingographic work have made reference to tuberculous salpingitis and endometritis. Two other authors wrote on the same subject but were uncertain of their own diagnoses, which were based merely by the presence of pulmonary tuberculosis in one[18] and of tuberculosis of the hip joint in another.[24] In other words, not until one has on hand anatomic and/or bacteriologic evidences of tuberculosis of the organs affected, it would seem incorrect to make such a diagnosis. So much more so when all clinicians know that patients with tuberculosis elsewhere do not necessarily have the same disease in their genitals.

Of the twenty-four articles, only ten authors[6, 14, 27, 26, 20 and 9, 25, 13, 10, 15, 16] published their x-ray pictures. Among them, the radiogram by Bond,[2] who alleged it to be shadows of calcium cast within the uterus and the tubes of a patient with appendicitis, was not a picture from injection of a contrast medium into the organs concerned. Thus, only twenty-seven published hysterosalpingograms of tuberculous salpingitis and endometritis are available for comparative description in the present study.

Since time does not permit any lengthy review or detailed description of the twenty-seven pictures obtained, suffice it to state here that the study of the topographic anatomy of the hysterosalpingograms is not an easy matter. It requires long experience and good judgment as to when the pictures are to be made, what contrast media to be used, and how the injection of the opaque material and the examination of the patient under the fluoroscope are to be practiced. Reuben Peterson has well expressed that it was easier to secure good plates than to interpret what the plates showed. Jameson even remarked in referring to tuberculous salpingitis and endometritis, "roentgenologically, pictures are very apt to be unintelligible or even worse, misleading." Both Gerlach and Madsen† concluded in their hysterosalpingographic work to have found no specific picture of the tuberculous changes. Neither did Schultze nor Kjehlberg point out in their voluminous monographs on the subject any characteristic features of tuberculous salpingitis and endometritis.

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*Abstract of an address, by invitation, of the guest speaker at the Seventieth Annual Meeting of the American Gynecological Society, Seigniory Club, Montebello, Quebec, June 17 to 19, 1947. For lack of space, only a portion of this address can be included in our pages.

†Since writing this article in June, 1947, the author had the pleasure to visit with Prof. Rydberg in Copenhagen, and learned from Dr. Madsen that he was about to publish his newer findings in his hysterosalpingographic work on tuberculous salpingitis and endometritis in November, 1947.

In my study of the twenty-seven hitherto published hysterosalpingograms of tuberculous salpingitis and endometritis, Robins and Shapira appeared to be the first to recognize some of the peculiar roentgenologic features of the disease, while Magnusson added many more and elaborated them into great details. In Magnusson's own words, the "finely jagged and ragged contours with small lumen defects and sometimes with abscess and fistula-like dilatations of the tubal lumen constituted the roentgenologic signs of tuberculosis." However, when one comes to review the twenty-seven pictures which I have at hand, one can point out many more characteristic features which the ten authors did not mention in their own descriptions. To be brief, three distinct and constant features have been found in common in all of them. First, the shadows show defective nonhomogenous filling of the contrast medium. Second, the tubes appear like thin stiff wires with irregular sacculations toward the fimbria. In the third place, in no case is there any free contrast medium in the peritoneal cavity. But, these are by no means all the points in the hysterosalpingograms in tuberculous salpingitis and endometritis, as I shall now point out in my own present observations.

Personal Observations

The present observations were obtained from six patients of 138 who had hysterosalpingograms in the Woman's Hospital during the period mentioned. All the six patients had two things in common. All came for sterility. All came during the silent stage of tuberculosis. All the x-ray tests were made by the author personally in order to secure the uniformity of technique and the complete removal of the element of individual variations in the evaluation of the tests. The eleventh day of the menstrual cycle was chosen for the test in all cases. The oil of lipiodol was the contrast medium. Very slight pressure was used to inject the oil. The injection was done under the fluoroscope. One cubic centimeter was employed for each injection according to the so-called "fractional method" of Joachimovitz and Hyams. During and after each injection, the hand was run over the suprapubic region with up and down movements in order to see the rise and fall of the shadows, the contractions and changes in the shape of these shadows, as well as their positions. At the same time, the patients were moved from side to side as well as obliquely so as to obtain a lateral or oblique view of the organs so filled by the contrast medium. Films were taken whenever necessary, and a plain film was always made before and twenty-four hours after the injection.

The accompanying illustrations are from the representative films made on the six patients upon whom the diagnosis of tuberculous salpingitis and endometritis was fully established. All six patients had operations; all operative specimens showed typical tuberculosis without any other disease; and in all cases animal innoculations from the operative material were made, although in only one did the animals show evidence of tuberculosis. In this patient, a positive culture of the tubercle bacillus was also obtained from the operative material.

Inasmuch as space does not permit a full description of all the films here, suffice it to summarize the salient features in a general way. First, in the plain films made before the injection of the contrast medium in four (Cases 1, 2, 3 and 4) of the six patients, x-ray opaque bodies were seen in their pelves. In Case 2, the shadow persisted even after a laparotomy. In Cases 2 and 3, fibrocalcareous adhesions were visible. Second, the filling of the uterine organ and the tubes was rather tardy. In the process of filling, no sign of con-

tractions was apparent. When filled, the cervical canal exhibited a fuzzy shadow which has been described "manelike" or "feathered" by various workers. The uterus appeared like a trumpet or a Voorhees' balloon, and its borders were shaggy and jagged. Its fundic shadow was invariably convex, and its lateral contour, likewise, bulging. The tubes, if filled, were filled in a jerky, fragmentary fashion so that their entire contour appeared to be beaded, segmented, and "fractured." They were stiff, wiry, thready, and drooped downward like a filament. There was often an abrupt ending of the filling process. The fimbria were pouchlike, saccular, and diverticular in shape. In the third place, the appearance of the entire contrast medium was uneven, nonhomogenous and simulating foreign bodies. Next, the stationary manner or the lack of spread of the contrast medium in the free peritoneal cavity and the frequent complete emptying of the filled tubes after twenty-four hours were quite characteristic. Last, as seen in Case 3, the imperfect filling of the organs might mislead one to think of a hypoplastic or a malformed uterus.

We may now pause for a moment in order to see just how such characteristic features in these hysterosalpingograms are produced. One must first remember that a hysterosalpingogram is but a shadow of the hollowed spaces (cavity or lumen) of the female internal genitals, and that the characteristics in the shadows are produced from the characteristic anatomy of these hollow spaces. Normally, the inner surfaces of these hollow spaces are lined by soft and distensible mucous membranes. They may be wrinkled but become smooth when distended. So, when a contrast medium is introduced into these spaces, they give rise to clear-cut and sharply outlined shadows in conformity with the shape, size, and position of the parts. These parts are muscular in nature and capable of movements or contractions by their tonicity. This tonicity may vary with the cyclic phases of menstruation. In other words, the shadows would exhibit not only the clear smooth and sharp outlines, contractile waves, and even thickness of the hollowed spaces, but also the rhythmical propagation of the contrast medium within the spaces. Any change or deviation from the normal must have come from a distinct pathologic process, namely, the disease of tuberculosis under present discussion.

As we all remember, the commonest mode of tuberculous invasion is by the blood stream. One must refer to Lisfranc for the pathologic anatomy of the tuberculous uterine cervix and to Kiwisch, that of the Fallopian tubes. Of late, Sutherland, Sharmann, Rubau, Eichner, Auerbach, and others have added considerable contributions to our knowledge on the subject. Speaking briefly the initial tuberculous bombardment is on the musculature of the tube, the commoner organ affected, or of the tube, or of both. Then, the foci of suppuration spread both ways to the mucous membranes and to the serosa. The route of spread appears to be mostly from tube to cervix and, within the tube itself, from fimbria to uterine cornua. The process is what Schramm and Simmonds called a bacillary catarrh. The mucous membrane is covered with thick ulcerative pads of caseation and, if old, partly organized and even calcified masses. Within the tube, this process does not develop evenly throughout its entire length. The abdominal end is more exudative, while the middle portion, patched with fibrin and the uterine end, studded with nodules. Thus, the tubal sphincters have become more prominent. The fimbria is occasionally open, but the ostium is closed. Hence the tubal lumen is essentially a passive way with the vegetations, the papillary excrescences and the organized granulation tissue protruding into it, which makes the passage of the contrast oil difficult. The x-ray shadow of such a passage is naturally stiff and wiry and, therefore, shows defective and nonhomogenous filling. When progressive caseation of the walls of the organ breaks through the serosa, they are studed with similar foci of fibrous and calcareous deposits. The stiffened organ becomes the so-called "*uterus sclereau.*"

Fig. 1.

Fig. 2.

Fig. 1.—Case 1. (No. 1349) A-P view after injection of 3 c.c. lipiodol.
Fig. 2.—Case 2. (No. 1385) A-P view after injection of 3 c.c. lipiodol.

Fig. 3.

Fig. 4.

Fig. 3.—Case. 3. (No. 2311) A-P view after injection of 2 c.c. lipiodol. (First test.)
Fig. 4.—Case 3. (No. 2311) A-P view after injection of 3 c.c. lipiodol. (First test.)

Fig. 5.

Fig. 6.

Fig. 5.—Case 3. (No. 2311) A-P view after injection of 2 c.c. lipiodol. (Second test.)
Fig. 6.—Case 3. Another view taken five minutes after Fig. 5.

Fig. 7.—Case 4. (No. 2415) A-P view, after injection of 3 c.c. lipiodol.

Fig. 8.

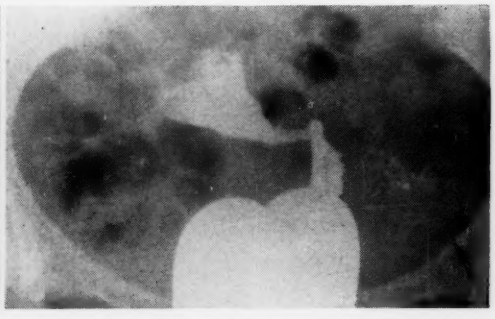

Fig. 9.

Fig. 8.—Case 5. (No. 3400) A-P view after injection of 1 c.c. lipiodol.
Fig. 9.—Case 5. (No. 3400) A-P view after injection of 2 c.c. lipiodol.

Fig. 10.—Case 6. (No. 3431) A-P view after injection of 2 c.c. lipiodol.

With these pictures in mind, one can easily understand why the contractility of the musculature of these organs has diminished or disappeared. Either the nerve elements have been injured, or the stiffened state of the muscles with numerous projecting masses of tuberculous tissue beyond the surface of mucous membranes has rendered the muscles mechanically impossible to contract. Such masses may thus hold and retain the contrast oil in the uterus even after a menstrual flow and after a biopsy curettage (Case 2).

Microscopically, one is struck by the absence of agglutination of the mucous folds. Slight adenomatous proliferation of the mucosa makes the lumen thready and filamentous. Thus, the not infrequent patency of the tubes will, therefore, explain the rare occurrence of pregnancy in either tube or uterus as reported by Stevenson and Wharton, Busby and Fischer, Schroeder and Rau, and others.

Differential Diagnosis of Hysterosalpingograms

The study of hysterosalpingograms cannot be complete without a sketch of an outline in making a differential diagnosis of a hysterosalpingogram that is representative of tuberculous salpingitis and endometritis from one that is indicative of other conditions. The former studies of Guthmann and Staehler, Menees and Miller, Phillipp and Huber, and Hyams have unfortunately failed to include the tuberculous and the normal in their publications. However, one cannot emphasize too strongly that the task must rest upon a radiologist and a gynecologist for well co-ordinated thought. In this connection, not only a precise clinical history and many technical points are important, but one must also remember that the uterine cavity and the tubal lumen are potential spaces. The linings of these spaces are different on different days of a menstrual cycle and in different regions. The injuries produced on them by diseases are variable. So, it may not be out of place to describe first a normal hysterosalpingogram on the eleventh day of the menstrual cycle, and then to compare it with those in other affections.

1. *Normal hysterosalpingogram.*—The findings in a normal hysterosalpingogram depend not only upon the age of the patient, but also on which cyclic day of menstruation the picture is made. When the endometrium is not completely healed after a menstruation, the oil injected may easily enter the veins. As pointed out, the day usually chosen for the work is the eleventh day. Here, the cervix is well filled like the shape of a smooth spindle. The uterus appears to be triangular with slight concavity over the fundic region, slight annular constriction at the site of Bandl's ring, with smooth, well-outlined and clearly cut borders. Both uterine cornua are pointed, with their sphincters shown or not shown. The shadows of the tubes on each side are seen to be composed of three segments: a horizontal straight line in their interstitial portion, a descending oblique and somewhat wavy line over their middle portion and a wavy ascending erectile line at their ampullary ends. Not infrequently, the ampula of one tube is seen to curve around the corresponding ovary and to be applied quite closely, exhibiting the so-called "*ovaria fossa Stellung.*" The contrast medium enters the free peritoneal cavity by the uterine and the tubal peristaltic action without any effort, and spreads over it like the paint brushed over a surface by the painter.

2. *Hyperplasia.*—Here the mucosa is thick and festooned into folds. When only a small amount of the contrast medium is injected by the fractional method, there are linear lines in the uterine cavity, as the micrographic work of Defrensne and of Raisz has amply demonstrated. Even the extreme enlargement of the mucosal folds would not show uneven, nonhomogenous shadow and there is no loss of the smooth outlines of the borders of the organ.

3. *Hypoplasia.*—Everything normal except in a diminished size. The tubes may be unusually long and somewhat wavy due to fetal convolutions. How-

ever, one should not confuse hypoplasia with tuberculosis of inner genitalia. Merletti found 28 tuberculous uteri in 80 hypoplastic patients. According to Heyneman, hypoplastic uterus predisposes localization of tuberculosis in the organ. But Sellheim appeared to be more reasonable in claiming that atrophy of the uterus is secondary to tuberculosis.

4. *Polypi and Submucous Myomas.*—Unless these lesions have become degenerated into a malignant condition, they usually give rise to well-outlined smooth and clear-cut shadows with ovoid, circular or elliptical contour according to the shape of the tumor. The tumors are invariably surrounded by the contrast medium. So, different films must be made in different positions.

5. *Retained Products.*—Retained products in the uterine cavity such as placental cotyledons are shown in the x-ray picture, according to Cotrim, resembling polypi or submucous fibromas. The intracavitary outlines may not be so smooth and the uterine cavity itself is slightly ovoid and large. The condition must not be confused with cancer. The clinical history in each is different.

6. *Ectopic Pregnancy.*—With decidua in situ, Mathieu has described the characteristic notched or toothlike outlines along the fundic region. But, a carefully taken history together with bedside picture of the patient is more important than an x-ray film.

7. *Endometriosis.*—The x-ray picture of endometriosis has been extensively studied by numerous workers. The peculiar feature here is the continuity of the mucosal lumen into numerous ramifications in the walls of the uterus or tube, or both. The contrast medium enters into these crevices to give rise to a picture like the roots of a plant or what Phillipp and Huber called "spitzer Zacken." As Madsen of Copenhagen has pointed out, there is a network of numerous pinhead-sized spots or of fine small threadlike channels leading from the main lumen. They look like venous channels, for they end within the musculature of the organ. Äkerland, too, showed the diverticular crypts and lacunar excrescences deep in the musculature. But none has any connection with the pelvic venous system. What Buteler compared this endometriotic picture to be more or less similar to that of tuberculosis is erroneous.

8. *Adenomyosis.*—It is not uncommon for chronic infection and adenomyosis to coexist in a uterus. Since tuberculosis is a form of chronic infection, some confusion has existed. With adenomyosis, the organs are naturally large. The uterus is irregularly deformed due to irregular distribution of the growth. Its contour is bulging but the outline is smooth. Also dots and diverticuli are present.

9. *Cancer.*—The clinical history is most important. If early, there is a localized narrowing of the cavity or lumen; then, elongation and enlargement. When craters and ulcerations occur, the margins are more irregular and elevated. There are small crevices. This is what Gerin-Lajoie called the crenated and fongous shadow.

10. *Calcified Shadows Other Than Tuberculosis.*—Numerous authors have called attention to the presence of opaque shadows in the pelvic cavity that are not necessarily tuberculosis. Stones in the ureters and bladder, teratoma, dermoid tumor, calcified fibroma, etc., are examples. Still many do not look for these things chiefly because they are not there clinically. In 1932, Bârcá described and called attention to the significance of radiopaque consolidation or even calcification in the Fallopian tubes. Therefore, it is always advisable to take a plain film first and to examine the patient after the injection in all directions so as to locate the position of such shadows.

11. *Chronic Endometritis and Salpingitis Other Than Tuberculosis.*—Other chronic infections of the uterus begin in the endometrium first. They do not alter so much of the muscular wall as the mucosa. Even affected, the mucous lining remains smooth. The cavity or the lumen may become widened and festooned.

12. *Malformation,* e.g., *uterus bicornis.*—This condition has given rise to much confusion with tuberculosis of the uterus and tubes. It is equally symptomless as many of the tuberculous cases. A casual examination of the x-ray films does not give much information. But, a bicornuate uterus should show two distinct shadows, complete or otherwise, of the uterine body as Rossi demonstrated. Their outlines and contours are smooth and free from any intracavitary irregularity or defect. The contrast medium remains homogenous. However, tuberculosis does exist in a malformed uterus as in the two cases of Brandess who also reported the co-existence in a case of malformed uterus of both tuberculosis and myoma. On the other hand, genuine tuberculosis of the tubes and uterus has been mistaken very frequently for uterus bicornis, as in the case of Martineau (his Fig. 7), Nahmmacher (his Fig. 16) and Magnusson (his Cases 8 and 10), as well as my own observation in Case 3. The contributions of Colloridi and Rouchy have discussed the topic in great details.

Summary

To summarize, unique and fairly constant topographic characteristics are seen in the hysterosalpingograms in tuberculous salpingitis and endometritis. Their pathogenesis has been speculated. An outline of differential diagnosis of hysterosalpingograms in various diseases has been presented. The presentation does not mean that all cases of tuberculous salpingitis and endometritis would present all the characteristics in their hysterosalpingograms. Never should it carry the idea that tuberculous salpingitis and endometritis be diagnosed by the x-ray pictures alone. It is hoped that the work may be done a little more frequently and extensively so that we can learn more out of it.

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AN EVALUATION OF PLASMA PITOCINASE DETERMINATION IN THE TOXEMIAS OF PREGNANCY*

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THE marked response to posterior pituitary hormone administration associated with the toxemias of pregnancy has been demonstrated.[1-3] The explanation of this phenomenon, however, like the cause of the toxemia itself, is unknown. Various workers have speculated as to the etiology of toxemia on the basis of either an increased secretion of the hormone or its ineffective inactivation and destruction in the body. Hofbauer (1918) was the first to relate an abnormal secretion of the posterior pituitary with the etiology of eclampsia and pre-eclampsia. This author later postulated the ineffective destruction of the posterior pituitary hormone by acetylcholine, resulting in the relative increase in the blood of the former.[2] The recovery of an antidiuretic and pressor substance in the blood of pre-eclamptic and eclamptic women by Anselmino and Hoffman[4] gave further emphasis to this relationship. Unfortunately, subsequent studies on this posterior pituitary-like substance by other investigators showed conflicting results.[5-10]

Recent work points to an enzymatic destruction of the posterior pituitary hormone by various tissue extracts (intestine, liver, kidney, muscle), as well as by dog, rabbit, and human blood.[11-13] The quantitative difference in the degree of inactivation of this hormone by nonpregnant and pregnant human sera was probably first suggested by Küstner,[14] who also stated that there was an increase of the hormone in serum of eclamptic patients. Von Fekete in 1932[15] likewise made the observation that pregnancy serum, as compared with the nonpregnant, showed increased inactivation of the hormone. A detailed study of the enzymatic nature of this hormone inactivator in serum and its increase with the age of pregnancy was reported by Werle and co-workers.[16, 17] Woodbury, et al.,[18] by the use of intrauterine pressure recordings in patients, confirmed these previous studies but did not find any quantitative difference between the neutralizing power of toxemic and normal pregnancy blood.

Page[19, 20] has devised a quantitative bioassay for a substance he named "pitocinase," which presumably is responsible for the enzymatic destruction of the posterior pituitary hormone. This substance, though not yet chemically isolated, has all the characteristics of an enzyme.

The present study was undertaken to determine whether there was any significant relation between the plasma pitocinase, and the diagnosis and prognosis of the toxemias of pregnancy.

*Supported in part by the Chicago Lying-in Hospital Fiftieth Anniversary fund for Research on Eclampsia.

Method and Results

All plasma pitocinase determinations were obtained according to the methods and calculations reported by Page.*[19-21] Pitocinase values as reported by Page have been considered as "normal," and our results are listed as either normal or low in comparison.

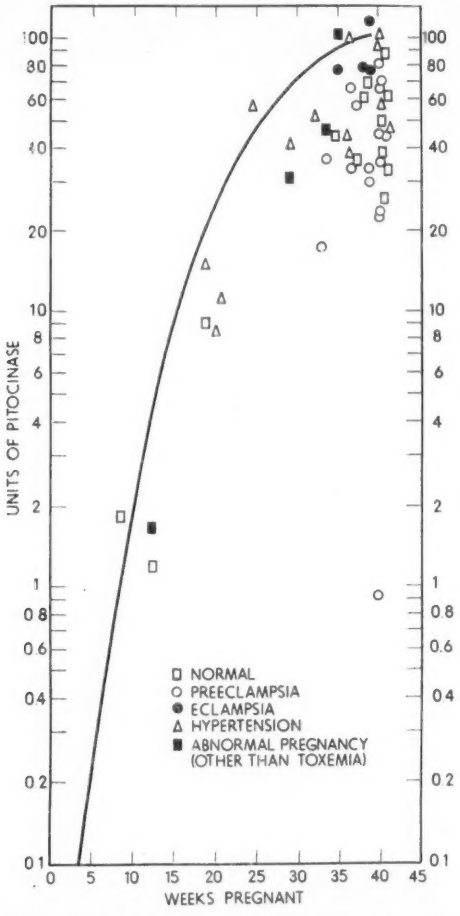

Fig. 1.—Pitocinase levels (compared with Page's curve).

A total of 50 pregnant patients (33 with toxemia) were studied. On a select group of patients, repeated determinations (two to four) were made at several days' interval, making a total of 83 pitocinase assays. Table I illustrates the results obtained. Figs. 1 and 2 show our values plotted against the pitocinase curve reported by Page. No attempts were made for pitocinase determinations in very early pregnancy, inasmuch as the main interest in the present work was the correlation of pitocinase levels with toxemia rather than as diagnostic of pregnancy. There was only one case studied of early pregnancy of eight weeks, and in this case a normal value was obtained.

The pitocinase levels obtained follow the pattern of Page. In general these values are lower than those he reports. In only three instances out of the 83 determinations did our values exceed the previously reported levels by 10

*Details in the technique were taken up in personal communication with that author.

TABLE I. PLASMA PITOCINASE LEVELS

DIAGNOSIS	TOTAL	SAME VALUES*	LOWER VALUES*
Normal pregnancy	13		
first half	3	2	1
second half	10	1	9
Pregnancy complicated by:			
diabetes insipidus	1	1	
placenta previa	1	1	
pyelitis	1	1	
hyperemesis gravid.	1	1	
Toxemias of pregnancy	33		
eclampsia	4	4	
pre-eclampsia	17	4	13
hypertension	12	4	12
Total	50	19	34

*Values compared with those reported by Page.[19, 20]

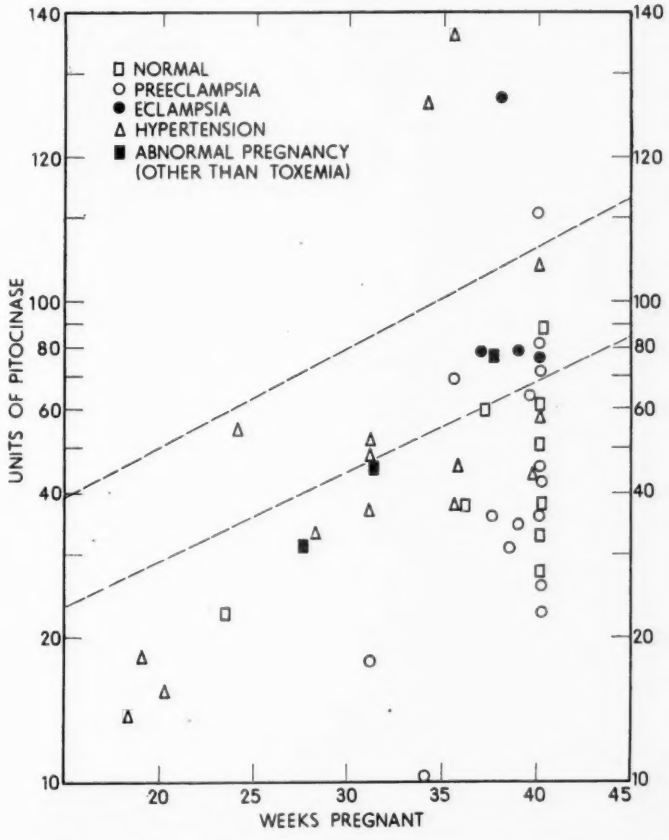

Fig. 2.—Pitocinase levels in the second half of pregnancy.

per cent (one eclamptic, one hypertensive with subarachnoid hemorrhage, and one with mild hypertension associated with erythroblastosis). As has been pointed out by Page, there is a wide variation of values in the toxemias without any significant difference between hypertensive and pre-eclamptic patients.

The levels in individual patients, as shown by repeat determinations, fluctuate without apparent relation to the clinical course of the patient. This is illustrated in Figs. 3 and 4.

Of the 33 toxemia patients studied, 21 were subjected to the pituitrin test as described by Dieckmann and Michel,[1] and the results of this test were correlated with the pitocinase levels, Table II. Samples for pitocinase determination were taken before the pituitrin test was done. In four of the patients who

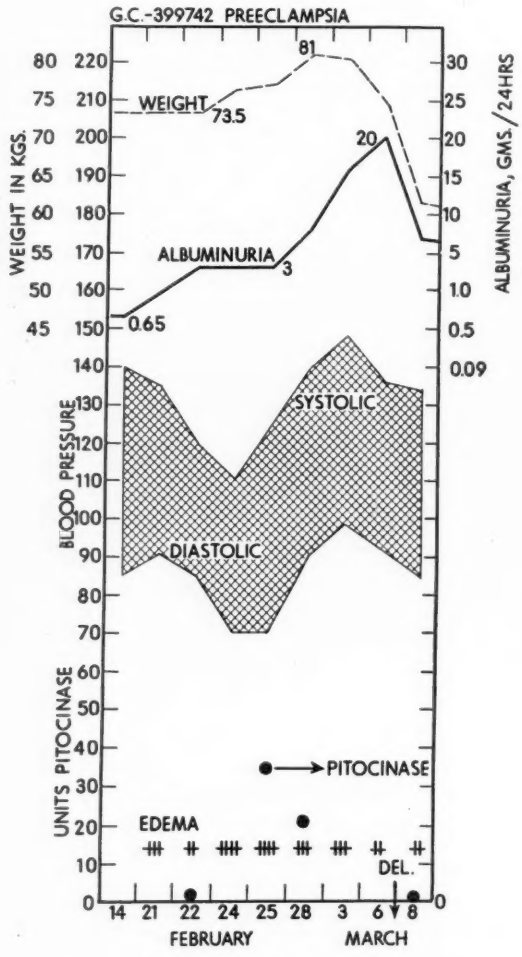

Fig. 3.

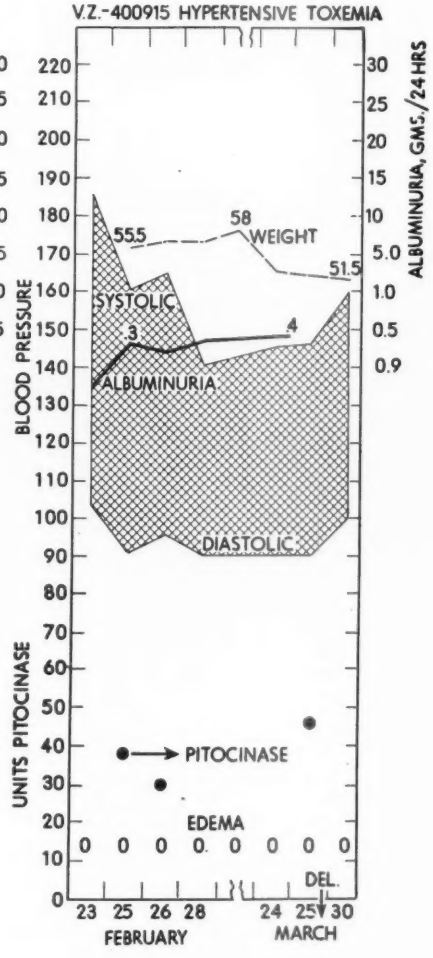

Fig. 4.

Fig. 3.—The pitocinase determinations (black dots) show no correlation with the clinical condition of the patient with pre-eclampsia.

Fig. 4.—The pitocinase determinations (black dots) show no correlation with the clinical condition of the patient with hypertensive toxemia.

showed a marked rise of blood pressure with the pituitrin test, a pitocinase assay was repeated within an hour after the test. Three of these patients gave lower repeat values and one showed an increase.

It is interesting to note that all the four eclamptic patients studied showed high pitocinase values, whereas pre-eclamptic and hypertensive patients gave lower and more scattered values.

TABLE II. A COMPARISON BETWEEN THE PITOCINASE LEVELS AND THE RESPONSE TO THE PITUITRIN TEST*

DIAGNOSIS	NO. OF CASES	POSITIVE TEST	PITOCINASE NORMAL†	PITOCINASE LOW†	NEGATIVE TEST	PITOCINASE NORMAL†	PITOCINASE LOW†
Eclampsia	1	1	1	0	0	0	0
Pre-eclampsia	15	8	2	6	7	2	5
Hypertension	5	1	0	1	4	1	3
Total	21	10	3	7	11	3	8

*Dieckmann and Michel.[1]
†Values compared with those of Page.[19, 20]

Discussion

There is sufficient evidence to suggest an enzymatic destruction of the posterior pituitary hormone in the human body. "Pitocinase" may well be that enzyme. As an organic catalyst, pitocinase, while accelerating the destruction of the hormone, should, ideally, be neither destroyed nor altered and should catalyze more than 200,000 times its weight of reacting material.[22] The results of the present study show that the pitocinase levels, in the toxemias of pregnancy, are not of any diagnostic or prognostic value. It seems that the hypersensitivity shown by pre-eclamptic and eclamptic patients to the posterior pituitary hormone is independent of plasma pitocinase levels. These findings are in accord with Woodbury, et al.,[18] who claim that normal pregnant as well as toxemic patients can rapidly inactivate pitocin and pitressin and that the hypersensitivity of the pre-eclamptic and eclamptic patients to these hormones is not due to a diminished ability to inactivate these substances. It is likewise reasonable to suppose that there is an optimum level of pitocinase for maximum destruction of pitocin, above which no further acceleration in the neutralization of the hormone takes place. The increase of pitocinase levels with the age of pregnancy may therefore be entirely unrelated to the sensitivity of certain pregnant patients to the posterior pituitary hormone.

Determinations for presence of an antihormone[22, 23] in normal pregnancy may explain the increased inactivation of solution of postpituitary by normal pregnancy serum. Further investigation into the various other enzyme systems during normal and toxemic pregnancy may uncover knowledge concerning their metabolism, and might even result in a diagnostic and prognostic guide for the toxemic state.

Summary and Conclusions

1. A total of 83 pitocinase determinations were made on 50 pregnant patients, 33 of whom were toxemic.

2. The enzymatic nature of the pitocin inactivation by pregnancy serum was confirmed.

3. In general, the range of pitocinase values obtained followed the curve reported by Page.

4. There is no significant difference in pitocinase values in hypertensive and pre-eclamptic patients. In both there is a wide range and a scatter of values.

5. No correlation was found between the pitocinase levels, and the clinical course of the toxemia and the hypersensitivity of the patient to pituitrin, as determined by the pituitrin test.

6. It is, therefore, concluded that plasma pitocinase levels in the toxemias of pregnancy are of no prognostic or diagnostic value.

I am indebted to Dr. Wm. J. Dieckmann for suggesting this problem and for making facilities available.

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LEUCEMIA AND PREGNANCY*

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FORTUNATELY, the coexistence of leucemia and pregnancy is rare. McGoldrick and Lapp,[1] reviewing the literature in 1943, cited 80 instances (including one of their own) with statistical evaluation of available data. Since that time I have been able to find 8 more reports, all of which seem sufficiently well authenticated to warrant inclusion in this study, which has as its purpose the presentation of two patients (with autopsy findings in one), review of reports since the last survey, and a few summary remarks concerning prognosis and management of this condition.

Presentation of Patients

CASE 1.—A 27-year-old primigravida housewife consulted Dr. F. S. Dunne on June 22, 1945. Her last menstrual period was Feb. 12, 1945, and the expected date of confinement was Nov. 19, 1945.

Except for recurrent attacks of pyelonephritis for the previous 16 years, her past history was irrelevant. In the three months prior to the last menstrual period she had lost 40 pounds in weight, but had noticed no unusual symptoms. She claimed that she was sensitive to procaine, cocaine, morphine, codeine, aspirin, sulfonamides, and barbiturates.

Physical examination revealed no abnormalities except for moderate pallor of the oral mucous membrane. The uterus was enlarged to 5 cm. above the symphysis pubis. The liver and spleen could not be palpated and there was no evident lymphadenopathy. The pelvis was of gynecoid type and was considered adequate for vaginal delivery. The blood Wassermann and Kahn reactions were negative. The hemoglobin value was 64.8 per cent (10.0 Gm.), red blood count 3.8 million, the white blood count was not done.

Despite progressive weight loss (a total of eight pounds during the period of gestation) she remained well until mid-August and mid-September when she had febrile episodes of pyelonephritis which responded adequately to courses of mandelic acid.

On Oct. 10, 1945 when she was admitted to the hospital she was having pains every five minutes which produced no cervical dilatation and which soon subsided. Examination of the blood done before discharge from the hospital the following day revealed a hemoglobin value of 71.4 per cent (11.3 Gm.); red blood cells, 3.4 million; and white blood cells, fifty thousand, two hundred.

The high leucocyte count was confirmed by a second examination on Oct. 15, 1945, which gave results indicative of chronic myelogenous leucemia, i.e., white blood cells 102,000 with promyelocytes 2 per cent, myelocytes 5 per cent, metamyelocytes 9 per cent, stab forms 20 per cent, segmenters 56 per cent, lymphocytes 5 per cent, eosinophiles 1 per cent, basophiles 2 per cent; platelets

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were abundant, and an occasional nucleated red cell was encountered. On this date there was no lymph node enlargement and no evidence of hemorrhagic or purpuric tendency. Because of the advanced pregnancy palpation was difficult and neither the liver nor the spleen could be felt, but the latter organ seemed to be moderately enlarged to percussion.

On Nov. 2, 1945, she was readmitted to the hospital, and the following day, sixteen days before the expected date of confinement, she was delivered of a living normal female infant (wt. 6 pounds 2 ounces) by elective cesarean section under gas-oxygen-ether anesthesia. Although no troublesome bleeding or oozing was encountered, she was given 500 c.c. of citrated whole blood during the operation. The spleen was palpated while the abdomen was open and judged to be 2 to 3 times the normal size.

The placenta measured 16 by 13 by 5 cm. and weighed 550 grams. Microscopic examination of the placenta showed numerous small areas of calcification throughout, and crowding of the sinusoids with small immature polymorphonuclear leucocytes, but no abnormal cells could be found in the fetal placental circulation.

The postoperative course for both mother and infant was uneventful. The infant showed no evidence of blood dyscrasia and weighed 5 pounds 14 ounces, when both were discharged from the hospital on the twelfth postoperative day.

On follow-up examination Dec. 7, 1945, the spleen was found to be enlarged to 7 cm. below the left costal margin; there was no detectable hepatomegaly, lymphadenopathy, or bleeding tendency. The patient stated that she felt very well. At that time the hemoglobin value was 69 per cent (10.7 Gm.), red blood cells 4.0 million, and white blood cells 72,000 with promyelocytes 3 per cent, myelocytes 10 per cent, metamyelocytes 14 per cent, stab forms 33 per cent, segmented forms 30 per cent, lymphocytes 6 per cent, eosinophiles 4 per cent; platelets were abundant.

General supportive measures and the one blood transfusion given at operation comprised the therapies employed.

Shortly after the follow-up visit in December the patient moved from Philadelphia. The details of her present status are not available, but both mother and child are reported to be doing well—one year after delivery. The mother is, in fact, pregnant again.

The following case is, to my knowledge, unique as the first reported instance of monocytic leucemia associated with pregnancy.

CASE 2.—A 35-year-old white para i, gravida i, housewife, seven months pregnant, was admitted to the Pennsylvania Hospital on April 30, 1946, because of hypertrophied gums, swelling of the neck, and mild sore throat. Her last menstrual period commenced Sept. 23, 1945, and June 30, 1946, was the expected date of confinement.

The present illness ostensibly began one month before admission when, shortly after the breaking of a decayed left upper third molar tooth, her gums rather abruptly became swollen and tender, and bled easily. With the persistence of these symptoms and the onset of tender submaxillary swellings, she was admitted for study and treatment.

Other than the usual childhood diseases, "virus pneumonia" in October, 1945, and an exacerbation of a chronic sinusitis with the present illness she had always enjoyed excellent health, and this pregnancy had been uneventful. Her previous pregnancy had ended with a cesarean section at term for placenta previa.

The physical examination revealed a well-developed and well-nourished woman in no apparent distress. The temperature was 100.8° F., pulse 120, respirations 18, and the blood pressure 122/ 76. Aside from moderate pallor the skin was not remarkable; there were no petechiae. The mouth disclosed pale mucous membrane, induration and swelling over the hard palate and the floor of the mouth, foul breath, and marked generalized tender hypertrophy of the gums on both buccal and lingual surfaces, almost covering several teeth, and presenting raw ulcerations in the area of the left upper third molar. (Fig. 1.) The submaxillary lymph nodes bilaterally were moderately enlarged, firm and tender, but no other lymphadenopathy was evident. Aside from the seven months' gravid uterus the remainder of the physical examination was not remarkable. There was no enlargement of the liver or spleen by palpation or by percussion.

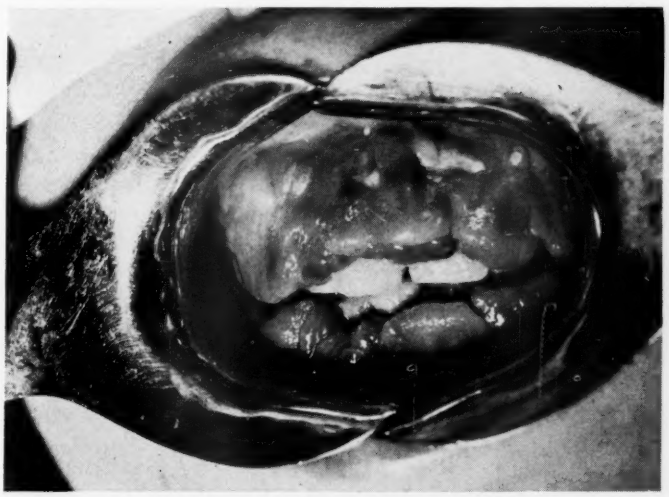

Fig. 1.—Showing the marked generalized hypertrophy of the gums.

Among the admission laboratory data was included a urinalysis which was negative except for a trace of albumin. The hemoglobin was 61.6 per cent (9.5 Gm.—Haden), red blood cells 2.1 million, and the white blood cells nine thousand, two hundred.

Course.—The patient was studied by the dental service and started on a high protein diet, daily intravenous administrations of 500 mg. of ascorbic acid and soluble B-complex vitamins, mouth irrigations with hydrogen peroxide, and parenteral penicillin therapy (120,000 units per day).

Her mouth continued to be painful but the oral hygiene improved and the submaxillary lymphadenopathy became less marked and tenderness over the glands decreased. A low-grade diurnal fever became persistent. Roentgenogram of the chest showed no evidence of disease of the lung.

Transfusions of whole blood were given on the tenth and fifteenth hospital days, and on May 17 the hemoglobin concentration had risen to 71.4 per cent of normal (11.0 Gm.), and the red blood cells to 4.0 million. The several total leucocyte counts done during these first weeks in the hospital were considered to be within the range of normal (9,200; 10,500; 8,250).

The patient was transferred to the Obstetrical Division on May 22, at which time the physical findings were essentially similar to those noted on

admission. The following day a complete blood count revealed hemoglobin 71.4 per cent (11.0 Gm.), red blood cells 4.0 million, white blood cells 21,000 with neutrophiles 7 per cent, lymphocytes 27 per cent, and 66 per cent blast forms (later identified by Dr. L. M. Tocantins as monoblasts). The platelet count was 310,000 per cubic millimeter, hematocrit 33 per cent, and the erythrocyte sedimentation rate was 41 mm. per hour (Wintrobe method). The bleeding time was 3 minutes, and the coagulation time was 4½ minutes. The tourniquet test and heterophile antibody test were negative.

The program of oral hygiene, ascorbic acid, and prophylactic penicillin therapies, and transfusions as indicated was continued. On May 29 a gingival biopsy was done. The section is illustrated in Fig. 2.

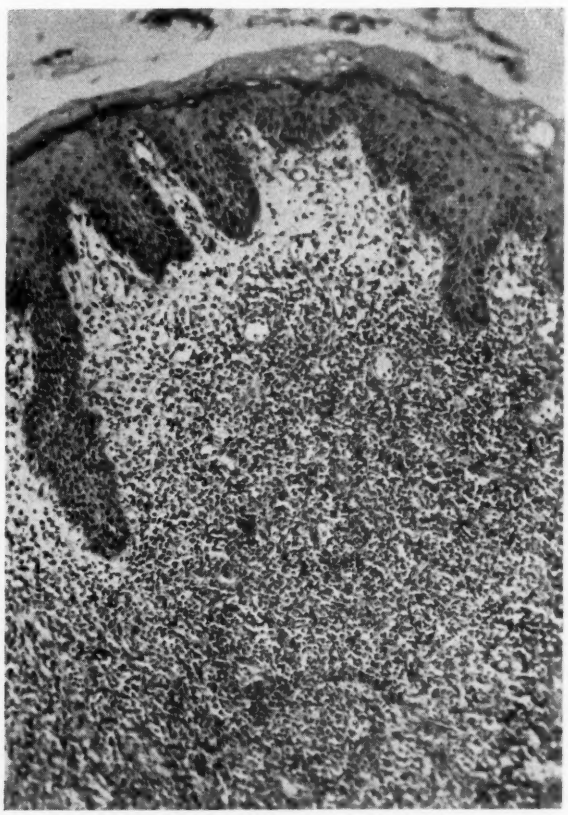

Fig. 2.—Biopsy of gingival tissue. The submucous stroma is densely infiltrated with mononuclear cells, separating the compact fibrous tissue bundles. (×130.)

By June 6, despite a blood transfusion of 500 c.c., the hemoglobin had fallen to 58.4 per cent (9.0 Gm.); and the white blood count was 35,600, with 2 per cent neutrophiles, 38 per cent lymphocytes, and 60 per cent monoblasts.

Cesarean section, first scheduled for June 12, was done on June 8, two hours after spontaneous rupture of the membranes. Under continuous spinal anesthesia the patient was delivered of a living normal male infant weighing 5 pounds 12 ounces. The baby was normal in all respects, with normal hematologic findings, and was discharged from the hospital 7 ounces over the birth weight on the twentieth day of life.

At operation, aside from a moderate amount of ooze from all cut vessels, hemostasis was not troublesome, and the patient seemed to withstand the procedure very well.

Although the gingival hypertrophy became less pronounced, from the time of operation until her death twelve days later her course was rapidly downhill, in spite of penicillin therapy (later sulfadiazine) and transfusions of whole blood. Abdominal distention, dyspnea, pallor, and weakness became profound, and her temperature showed progressive elevation and irregularity. On June 15 the liver and the spleen were palpably enlarged, and the patient complained of pains in the left upper quadrant of the abdomen. On this date the hemoglobin was 68.1 per cent (10.5 Gm.), white blood cells 65,000, with a differential count essentially as before. The platelet count was 100,000, the bleeding time 30 seconds, the hematocrit 30 per cent, and the sedimentation rate was 54 millimeters per hour.

On June 18, marked air hunger supervened and petechial hemorrhages were noted. Despite transfusion and oxygen therapy, she expired on June 20.

Complete postmortem examination was performed seven and one-half hours after death by Dr. D. N. Twaddell.

Postmortem Examination.—Pathological diagnosis, acute monocytic leucemia, with leucemic infiltration of all organs, monoblastemia, petechial hemorrhages of all organs, acute ulcerative gingivitis, multiple infarcts of the spleen, pulmonary edema, and postpartum involution of the uterus.

External Examination.—Numerous petechial hemorrhages were seen over the entire body. The skin was of a dusky hue but was not jaundiced. There was a healing operative incision in the lower mid-abdomen. A few soft submaxillary nodes were barely palpable, but elsewhere the superficial nodes could not be felt. A blood tinged froth was present in the oral and the nasal passages. The gums were markedly swollen and hemorrhagic, with extension of the margins progressively along the teeth. This hypertrophy of the gums appeared about the upper and the lower teeth and on both buccal and lingual surfaces. On the roof of the mouth the mucous membrane was involved as far as the soft palate. The breasts were of firm consistency throughout. The abdomen was slightly distended, and in the suprapubic region there was a fullness occasioned by the enlarged involuting uterus. There was no peripheral edema.

Internal Examination.—There were petechial hemorrhages over both parietal and visceral peritoneal and pleural surfaces. The peritoneum in the region of the operative site was completely healed.

Bone marrow: The bone marrow of the ribs and vertebral column was remarkably pale but otherwise not grossly abnormal.

Lungs: The lungs were unusually firm throughout, and on cut section both upper lobes and the right middle lobe (and, to a lesser extent, the lower lobes) exhibited a considerable amount of diffuse infiltration and areas suggestive of consolidation.

Heart: Except for scattered subepicardial hemorrhages the heart was grossly normal.

Spleen: The spleen was enlarged to 4 cm. below the costal margin, weighed 1,010 Gm., and presented a tense congested capsule with many diffuse hemorrhages; on cut section marked congestion and scattered hemorrhages were seen; Malpighian bodies and trabeculae were not discernible.

Gastrointestinal tract: The stomach was moderately distended with gas and showed many submucosal hemorrhages but no ulcerations. The small intestine was collapsed and contained a considerable quantity of dark coagulated

blood, particularly in its distal segments; throughout its length Peyer's patches were markedly enlarged, especially in the region of the ileocecal valve where several patches measured 1.5 cm. in diameter and were elevated 4 mm. above the remainder of the surface of the mucous membrane. The ileocecal valve itself was the site of ulceration with accumulation of a fibrinous, diphtheritic, markedly hemorrhagic exudate, but there was no obstruction. The mesenteric lymph nodes were firm but only slightly enlarged.

Liver: The markedly enlarged liver weighed 2,600 Gm. and was of a very soft consistency; there were no hemorrhages but a leucemic infiltration throughout all the portal areas was obvious.

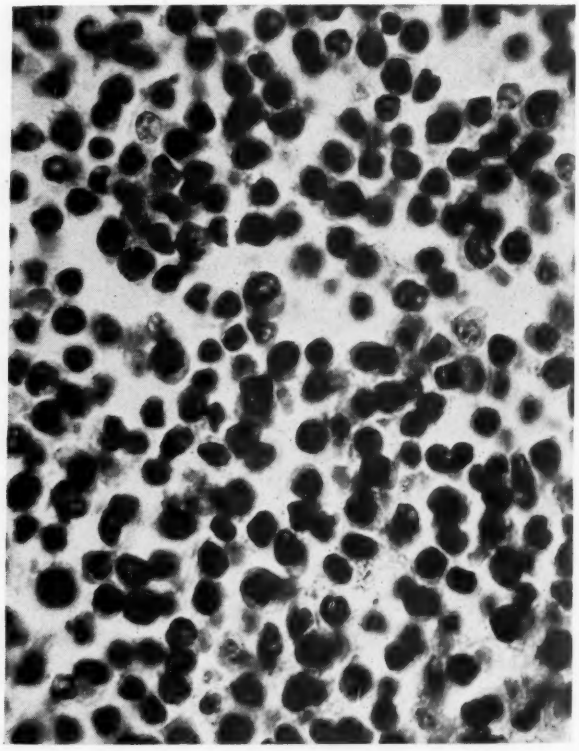

Fig. 3.—Photomicrograph of a section of one of the uterine blood vessels, showing the typical cell found in the blood and in the widespread infiltrations. Oil immersion. (×1225.)

Kidneys: The kidneys, large and swollen, exhibited cortical petechiae and widespread leucemic infiltration of both cortical and medullary tissue.

Pelvic organs: Both ovaries were large and firm. The uterus was symmetrically enlarged and the operative incision in its substance was well healed.

Brain: Examination of the brain revealed no gross abnormalities save for two small areas of recent hemorrhage in the dentate nucleus of the left cerebellar hemisphere.

Microscopic Examination.—The striking feature of the microscopic examination was the widespread and diffuse infiltration of all organs and tissues studied—breast, thymus, heart, lungs (Fig. 4), diaphragm (Fig. 5), spleen (Fig. 6), peritoneum, intestines, mesentery, pancreas, liver, gall bladder, adrenals, kidney (Fig. 7), pelvic organs, lymph nodes, thyroid, bone marrow,

gingivae, tongue, and brain. The typical cell was nonpleomorphic and averaged 15 micra in diameter with a single oval to reniform vesicular nucleus and a large amount of eosinophilic cytoplasm (Fig. 3).

Heart: There was a generalized infiltration of the epicardium with the neoplastic cells which appeared in small clusters throughout the fatty tissues, the interfibrillary tissue of the myocardium, and the endocardium.

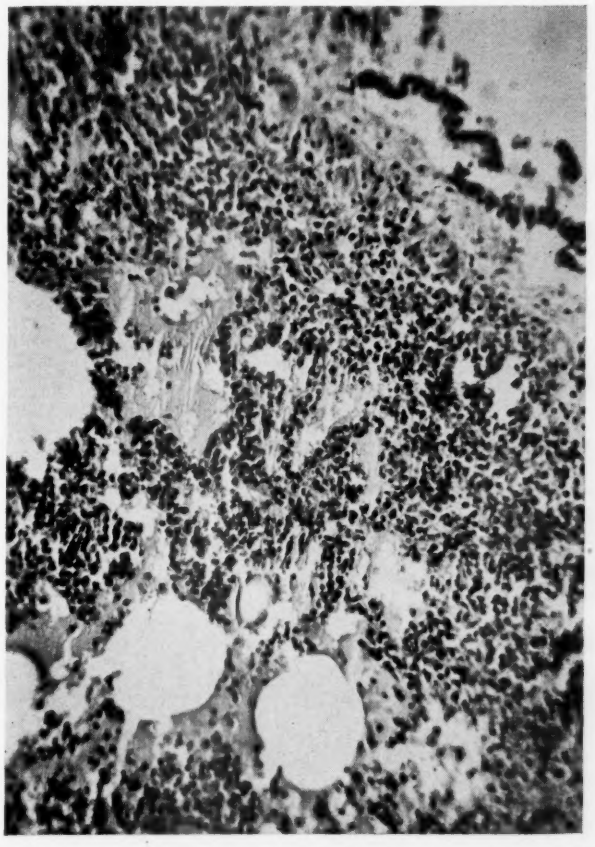

Fig. 4.—Photomicrograph of a section of the lung showing invasion of alveoli and interstitial tissue with monoblasts. (×200.)

Lungs: Similar pathologic changes were seen in the lungs with collections of mononuclear cells in the subpleural areas, within blood vessels and small bronchi, and along the septa and alveolar walls; there was considerable hemorrhage throughout the lung parenchyma with small areas of necrosis, and alveoli containing edema fluid, erythrocytes and monoblasts.

Pelvic structures: Of the pelvic structures the ovarian stroma, Fallopian tubes, serosa, myometrium, venous sinusoids, and necrotic decidual tissues were heavily invaded by islands of leucemic cells, and there were monoblasts engulfed in the meshes of fibrin of the intrauterine clot. Unfortunately, the placenta was inadvertently discarded.

Lymph nodes and bone marrow: The architecture of both medullary tissue and lymphoid follicles of the lymph nodes and the spleen was markedly distorted and in the vertebral and costal bone marrow the fat was entirely absent, the space being occupied by densely packed mononuclear elements with only occasional myeloid and erythroid cells apparent.

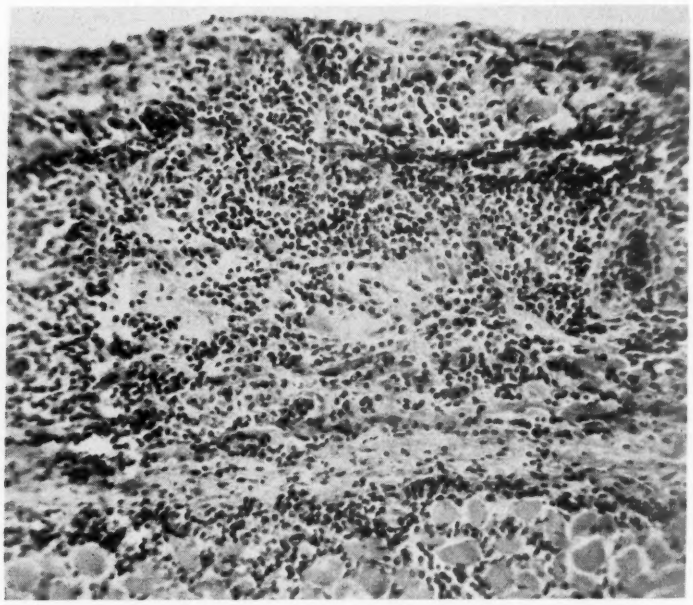

Fig. 5.—Photomicrograph of a section of diaphragm, with infiltration of the interfibrillary tissue. (×200.)

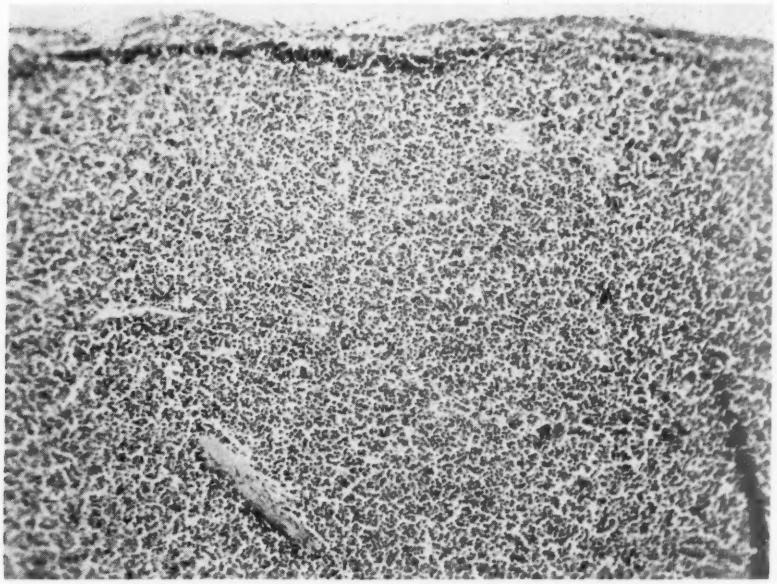

Fig. 6.—Photomicrograph of a section from the spleen. Distortion of the normal architecture is clearly seen. (×130.)

Gingivae: The gingivae, by biopsy and by necropsy, exhibited dense infiltration of the submucous stroma with mononuclear cells, and areas of ulceration but no polymorphonuclear leucocytes were seen. (Fig. 2.)

Brain: Even the brain was not spared, with scattering of monoblasts in the perivascular tissue, cerebrum, cerebellum, and the pituitary gland.

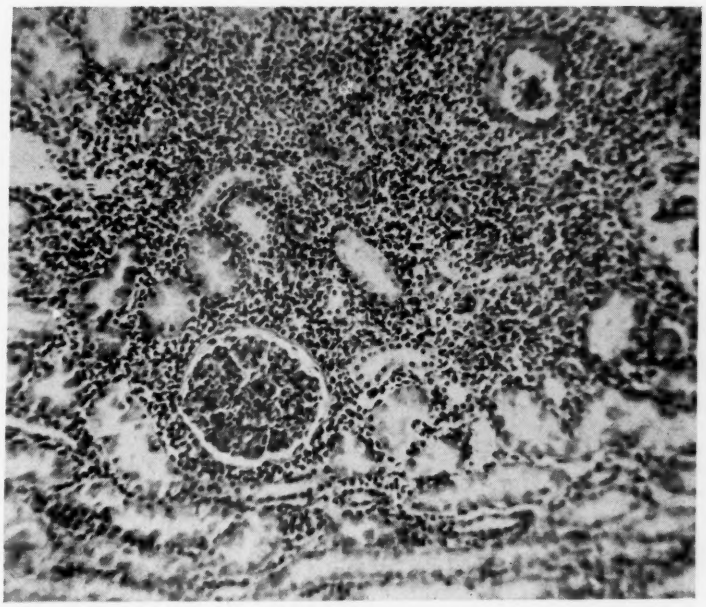

Fig. 7.—Photomicrograph of a section of kidney, showing the heavy invasion of stroma and glomeruli. (×200.)

Comment

In the first patient it seems probable that the leucemic state antedated conception and gestation by at least several months, while in the second instance onset during pregnancy seems likely. The course and the findings at autopsy in the patient with acute monocytic leucemia, though unique in obstetric literature, are in close accord with previous reports of this disease,[2, 3] the natural history of which was apparently not altered by the complicating pregnancy.

Similarly, there are numerous discussions in the literature of the significance of oral lesions in leucemia.[2-11] While gingival hypertrophy and ulceration do occur occasionally in other types of leucemia,[5, 10, 12] and the oral manifestations of all types of acute leucemia are said to be similar,[7] these changes have been observed in 52 per cent.[5] to 80 per cent[11] of cases of acute monocytic leucemia and are considered by some to be so characteristic that the diagnosis should be suspected on clinical grounds alone.[9, 11, 13] It is also noteworthy, though familiar, that pathologic changes in the gums may be the first manifestations of the disease, as in Case 2.

The medical management of both of these cases was of a supportive nature. Although it has been suggested that Fowler's solution or even irradiation could be administered with relative impunity during gestation,[14-18] it was felt that the

TABLE I. TABULATION OF CASES REPORTED SINCE THE LAST REVIEW OF THE LITERATURE[1].

CASE NO.	AUTHOR	YEAR	AGE	PARA	RELATION OF ONSET TO GESTATION	PERIOD		HEMORRHAGE	RESULTS		TYPE OF LEUCEMIA
						GESTATION	DELIVERY				
						WHEN	HOW		MOTHER	CHILD	
1	Holmgren[20]	1944	40	v	1½ yr. prior	Term	Spont.	None	Lived	Lived	Chronic myelogenous
2	Hochman[16]	1944	25	i	22 mo. prior	2 mo.	Induced abortion	None	Died 4 mo. postop.	Nonviable	Chronic myelogenous
3	Hochman[16]	1944	23	i	1½ yr. prior	Term	Spont.	None	Died 10 mo. post partum	Lived	Chronic myelogenous
4	Applebaum[19]	1944	29	0	3 mo.	7½ mo.	C. sect.	—	Died several hours post partum	Stillborn	Acute myelogenous
5	Angelucci[17]	1944	22	0?	4 mo. ?	Term	Forceps	None	Lived	Lived	Chronic myelogenous
6	Miles and Wheeler[18]	1945	30	viii	6 mo. prior?	Term	Spont.	None	Lived	Lived	Chronic myelogenous
7	Miles and Wheeler[18]	1945	30	ii	Prior	8 mo.	Spont.	Yes	Lived	Lived	Chronic myelogenous
8	Bright and Hayes[21]	1946	23	i	4-5 mo.	Term	Spont.	None	Died 3 mo. post partum	Lived	Acute lymphatic

absence of symptoms in the first patient interdicted such treatment. There is no known therapy that alters the course of acute leucemia; irradiation is apparently seldom of even temporary aid and may cause severe reactions[2, 4]; blood transfusions may be of transient value.

The indication for cesarean section in the second patient was a previous section, while in the patient with chronic leucemia it was the maternal disease which indicated this method of delivery. The validity of leucemia as an indication for a section is not upheld by previous observations in the literature. Moloney et al.[15] reported a woman with chronic myelogenous leucemia successfully delivered by section (the indication being uncontrollable toxemia) without apparent ill-effect on mother or child. This same author was able to find reports of three other leucemic women delivered by this method; two of the infants thus obtained were stillborn, and all of the mothers died within eleven days after delivery. Appelbaum[19] describes a case of acute myelogenous leucemia with cesarean delivery at seven and one-half months; the infant was stillborn, and the mother died several hours post partum. All of which tends to corroborate the statement of Grier and Richter[14] that interference with pregnancy does not help the mother in either acute or chronic leucemia, that it only tends to produce premature and nonviable babies, and that in the acute form it shortens the mother's life.

A rapid downhill course following delivery has been previously reported.[1] Although this was true for the second patient, it would be unwise to draw any conclusions in view of the precipitous course of monocytic leucemia.

Premature labor has been seen in the majority of cases, but severe hemorrhage, post partum or during delivery by any method, has been uncommon—9 instances of 88 with 3 deaths.

With critical review of the literature, it is safe to conclude that pregnancy has little, if any, effect on the course of leucemia. Conversely, however, McGoldrick[1] found maternal mortality 100 per cent and fetal mortality 60 per cent for the acute forms, while the mortality was 36.5 per cent and 16.4 per cent, respectively, for the chronic types. It is interesting that a leucemic mother has never been reported as producing a leucemic child.

The eight cases that have accumulated since McGoldrick and Lapp wrote their paper do not warrant statistical re-evaluation of the problem. Following the scheme of Grier and Richter, these reports are presented in Table I.

Summary

1. The literature has been reviewed and two cases added, bringing the total number of reported cases of pregnancy associated with leucemia to ninety.

2. A case of chronic myelogenous leucemia complicated by pregnancy, with the mother still living more than a year after delivery, is presented.

3. A fatal case of acute monocytic leucemia complicating pregnancy, with a discussion of necropsy findings, is presented. No similar case has been found in the literature.

4. Leucemia per se does not require any special obstetric management.

5. On the basis of reported cases leucemia is not transferred from mother to child.

6. Although in the two cases here reported no unusual bleeding was encountered, it must be recalled that of the eighty-eight previously reported cases serious hemorrhage occurred in nine, with three deaths attributable to this cause.

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THE EFFECT OF EQUINE GONADOTROPIN (GONADOGEN) ON THE HUMAN OVARY

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THE gonadotropic activity of equine gonadotropin and the experimental production of ovulation by this agent in the human being have been the subject of much investigation in the past decade. The findings, however, have been varied and contradictory. The research of Aschheim and Zondek[1] and Smith and Engle[2] in this country has shown that ovarian function is regulated by the anterior lobe of the pituitary. The demonstration of the gonadotropic activity of pregnancy urine and of extracts of the anterior lobe of the pituitary gland soon led to the experimental production of ovulation in laboratory animals. This gave impetus for similar investigations in the human female.

Using chorionic gonadotropin, Campbell,[3] Geist,[4] Hamblen,[5] Geist, Gaines, and Salmon,[6] and others were unable to demonstrate the production of growth and maturation of the Graafian follicle and ovulation in women. Hamblen[7] and other investiagtors also failed to demonstrate ovulation in women, following the administration of anterior pituitary extract.

A new source of gonad-stimulating hormone was discovered in 1930 by Cole and Hart[8] in the blood of pregnant mares. It resembled extracts of the anterior pituitary gland in its physiologic properties, by producing follicular development, ovulation, and corpus luteum formation in hypophysectomized animals. Gross and Cole,[9] Catchpole and Lyons,[10] and Hamburger[11] were successful in producing fertile ovulation in rats, ewes, sows, and cows by the injection of pregnant-mare serum. In 1938, Davis and Koff[12] reported that they produced ovulation in women by the intravenous use of pregnant-mare serum in half of their cases. This work was confirmed by Siegler and Fein,[13] who reported artificial ovulation in 16 of 30 women. Hartman,[14] working with adult monkeys, found a reasonable certainty of stimulated ovulation in only 7 of 104 cases. Watson, Smith, and Kurzrock[15] reported that they were able to stimulate follicular development in women with the hormone of pregnant-mare serum, but could not show ovulation in any of their cases. Geist, Gaines, and Salmon[16] reported the results of equine gonadotropin administered intravenously or intramuscularly in 22 women. In no instance was conclusive evidence of artificially induced ovulation found. Brewer, Jones, and Skiles[17] also administered equine gonadotropin intramuscularly to 24 women subjected to laparotomy, and reported failure to induce ovulation. Greenblatt[18] reported stimulation of the various components of the ovary following gonadotropin administration, but orderly maturation did not occur.

As studied by endometrial biopsy, Griffith and McBride[19] reported induced ovulation with equine gonadotropin in 7 of 8 patients with anovulatory cycles. On the other hand, Erving, Sears, and Rock[20] reported no evidence of stimulation in the ovaries in 16 anovulatory patients as determined by endometrial biopsies.

Read at a meeting of the Brooklyn Gynecological Society, October, 1946.

TABLE I. EFFECT OF GONADOGEN UPON OVULATION

CASE	AGE	MENSTRUAL INTERVAL	INJECTION DAY OF CYCLE	NO. OF UNITS	OPERATION DAY OF CYCLE	PREOPERATIVE ENDOMETRIAL BIOPSY	CURRENT C. L.	INDUCED OVULATION
1	42	30	23	60	24	Atrophic, interval fibroid	+ Effl.	0
2	25	28	16	60	17	Interval	+ Cong.	0
3	31	12-20	7	60	9	Postmenstrual	0	0
4	44	26-28	21	60	22	0	0	0
5	34	14-21	17	60	22	0	+ Invol.	0
6	48	28	23	60	25	Initial premenst.	+ Late vasc. (double)	0
7	45	28	19	60	25	0	+ Cong.	0
8	40	26-28	14, 15	60, 60	20	0	+ Late vasc.	0
9	38	28	23	60	25	Mixed premenst.	+ Effl.	0
10	44	Irreg.	22	60	23	Premenstrual	+ Effl. (double)	0
11	49	Irreg.	8	60	10	Postmenstrual	0	0
12	38	28	26	60	28	Premenstrual	+ Effl.	0
13	40	28	22	60	23	0	+ Effl. (double)	0
14	47	Irreg.	?	60	27 hours after inj.	Prolif., late	+ Cong. (double)	0
15	45	26-28	7	60	9	Prolif.	0	0
16	45	30	9	60	15	Postmenstrual	+ Cong.	0
17	34	28	6	60	9	0	0	0
18	37	28	7	60	9	0	0	0
19	35	14-42	14	60	19	Prolif., late	+ Early vasc.	0
20	33	Amen.	—	60	24 hours after inj.	Uterus absent	+ Vasc. (double)	0
21	42	27	10, 12	60, 30	14	Early prolif.	0	0
22	36	14-28	12	60	13	Prolif., late	+ Early vasc.	0

It is evident that the present status of equine gonadotropin is far from clear. Hamblen[21] states, "Equine gonadotropin has the ability to stimulate follicular activity in the human being and in the monkey, but ovulation and corpus luteum formation are not induced." On this basis, for the treatment of anovulatory failure, he has supplemented equine gonadotropin for its follicle-stimulating properties by chorionic gonadotropin for its luteinizing ability.

Material

Because of many conflicting reports obtained, we felt it wise to review by a new study the actual effects on the human ovary by equine gonadotropin. Twenty-two women were selected for this study. All patients utilized in this investigation, with one exception, were subjected to laparotomy because of a fibromyoma uteri. Case 20 had had a previous hysterectomy and left salpingo-oophorectomy. Laparotomy was performed for a parovarian cyst. The right ovary was originally left in situ.

The ages of the women varied from 25 years to 49 years. One patient was 25 years of age. There were 5 patients in the 31 to 35 age group, 5 patients in the 36 to 40 age group, 8 patients in the 41 to 45 age group, and 3 patients in the 46 to 49 age group.

The menstrual periods had been regular except in 7 patients, who had recent menometrorrhagia. One patient (Case 20) had had long-standing amenorrhea after hysterectomy.

Prior to laparotomy, a vaginal smear and endometrial biopsy were performed. Vaginal smears were not contributory. After preliminary skin and ophthalmic sensitization tests, the equine gonadotropin was administered intravenously in varying dosage and for a variable period of time prior to operation. The average dose was 60 Cartland-Nelson units of Gonadogen. In 2 cases, 90 units were administered, and in one case each, 100 and 120 units of Gonadogen. The interval between administration of the Gonadogen and operation varied from 24 hours to 146 hours with an average of 60 hours. The administration of the drug and laparotomy were performed at different times during the menstrual cycle. The drug was administered in the first half of the menstrual cycle in 5 cases, in mid-cycle in 4 cases, in the second half of the cycle in 12 cases. At operation, the uterus, both ovaries, and tubes were removed whenever feasible, and sections were taken from the uterus, to study any changes in the endometrium, and from all cystic areas in all ovaries. The findings are summarized in Tables I and II. Basically, as will be seen from the records, ovulation was not observed.

We can now proceed with a summary of changes induced in the human ovary as observed after Gonadogen:

Stromal Changes.—Universal edema of the ovaries was not observed, either on gross or microscopic examination, but occasionally was pronounced in the theca externa about follicular cysts. Hyperemia, however, was common and the entire organ often assumed a pink-gray appearance. This was especially noted in 12 of the cases. Perifollicular and intrafollicular hemorrhage was a striking finding and occurred in 16 cases of the group (Fig. 1). The numerous, tense, red or red-blue cysts studding the cortex were a dominant finding after Gonadogen stimulation. Pseudodecidual changes of the stromal cells were noted in Case 1. Clusters of fusiform and round stromal cells with pink or blue-pink cytoplasm and a central vesicular nucleus were noted in the cortex just beneath the tunica. They resembled similar collections seen in the normal ovary at the end of pregnancy.

Vascular Apparatus.—In practically all cases, engorgement of capillaries was marked. It reached its zenith in the vessels of the theca externa of the

TABLE II. EFFECT OF GONADOGEN ON FOLLICULAR APPARATUS OF HUMAN OVARY

CASE	FOLLICULAR HEMORRHAGE			PSEUDOLUTEINIZATION OF GRANULOSA CYSTS OR CURRENT MATURING FOLLICLE	THECA INTERNA CYSTS	THECA INTERNA HYPERTROPHY	TRUE LUTEINIZATION OF UNRUPTURED FOLLICLE	UTERINE ENDOMETRIUM
	PERI-FOLLICULAR	INTRA-FOLLICULAR	INTER-STITIAL					
1		+	+				+	Interval
2	+	+				+		Late interval
3	+		+	Old—f				Prolif.
4		+	+	Old—f	+			
5	+	+		Recent				Interval
6	+				+	+		Premenst.
7	0	0	0	0	0	0	0	Late interval
8			+		+	+ in corpora fibrosa		Initial premenst.
9	+	+	+	Old	+			Late premenst.
10	+		+		+			Premenst.
11				Current marked	+			Early interval
12						+		Premenst.
13		+			+			Late premenst.
14	+	+	+					Late interval
15	+			Current—marked		+		Interval
16	+							Interval
17	+	+		Old and recent		+		Interval
18	+	+	+	Old				Interval
19	+		+	Recent		+		Late interval
20		+			+	+		?
21	+			Recent		+		Early prolif.
22	+			Recent				Late interval

more recent follicular cysts. Diapedesis resulted in free red cells in the edema fluid about the cysts (Fig. 2). Actual rupture with resulting interstitial hemorrhage was frequent, the escaping blood breaking through the overlying columns of the theca and granulosa cells to reach the cavity of the cyst. We do not feel that convolution of the pseudoluteinized follicle is due to pressure by the engorged thecal vessels upon the overlying theca and granulosa layers. Reference to resultant interstitial perifollicular and intrafollicular bleeding has been made above.

Fig. 1.—Ovaries after Gonadogen. Perifollicular and interstitial bleeding is prominent.

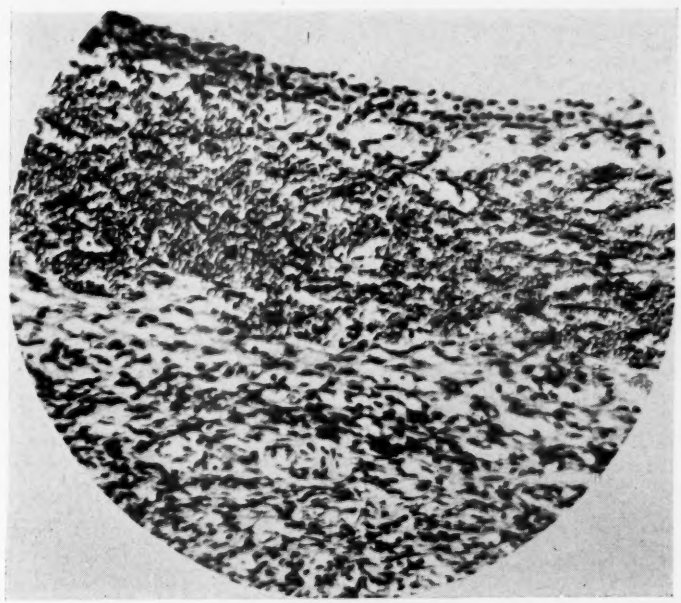

Fig. 2.—Case 6, right ovary. Old follicular cyst with perifollicular bleeding and edema.

Follicular Apparatus.—In this study we have been unable to find evidence of Gonadogen stimulation of the follicle, either by (a) multiplication in the number of maturing follicles or (b) the acceleration in tempo of the ripening

of an individual follicle. In 5 cases (Nos. 2, 13, 14, 15, and 20) maturing follicles with discus proligerus were observed. The ovum was seen in 3 cases (Nos. 2, 14, and 15). In Cases 2 and 14, the ova were disintegrating. The follicles were in association with a corpus luteum of congestion and, therefore, attributable to the current cycle. The time of Gonadogen injection and the menstrual dates further support this view. In Case 13, the maturing follicle with a discus was associated with double corpus of efflorescence in the same ovary but no ovum was seen in two or three sections studied. In Case 20, a maturing follicle with an ovum in the discus was found in the right ovary, which was also the seat of a double corpus of vascularization. Whether this was an early atresic follicle which began maturation concurrently with the two others transformed into corpora cannot be told. The gap in the knowledge of the time required for disintegration of an ovum and its discus in an unruptured follicle allows no answer. In all these cases, the granulosa layer of the maturing follicles showed an increment of cell cytoplasm and the theca interna was especially prominent. Theca changes were especially marked in Cases 2 and 20.

"Pseudoluteinization of follicle cysts," so designated by Greenblatt, was observed in Cases 11 and 15 (Figs. 3 and 4). These are currently-maturing follicles and are often mistaken for newly ruptured follicles in the incipient stage of lutein transformation. Indeed, this finding may have been the pitfall for those investigators who ascribed follicle maturation and rupture to equine gonadotropin. Both have compressed cavities with an irregular margin, but in the normally ruptured follicle a stigma or "punktum" is grossly present. The cavity is truly collapsed and the lining shows marked dentation. The normal early lutein cell is granular with pink acidophilic cytoplasm. The nucleus is round and deeply staining. The cell body soon elongates (Fig. 5). Clear lutein cells are not seen in a normal corpus until vascularization is reached, but at this time the corpus is grossly seen beneath the tunica, even when not dendritic. On section, the wide central cavity and its bloody coagulum contrast with the convoluted gray-yellow lutein lining. The clarity of the cell in the "pseudoluteinized follicle" is the initial episode and begins in the cell cytoplasm prior to rupture of the follicle. It is attributable to the excess lipoid deposit resulting from perifollicular engorgement. The irregular hypertrophy of the cells due to lipoid deposition may well be the cause of the irregular configuration of the central cavity. In sections after scharlach R stain, we have seen similar lipoid deposits in the granulosa cells of follicle cysts. Intracellular edema is excluded by the uniform staining and lack of nuclear and membranous changes of the cell body. It is worthy of note that those instances of "pseudoluteinization" were in ovaries injected on the seventh and eighth day of the cycle and that a corpus luteum of the current cycle was not observed. Whether an artificially lipoidized follicle can proceed to maturation, rupture, and liberation of a normal ovum cannot be told.

True luteinization in an unruptured follicle was noted only once (Case 1, Fig. 6). In the same patient, clusters of decidua-like cells were noted in the ovarian cortex. A corpus luteum of efflorescence of the current cycle was present in the (other) right ovary. Grossly, the luteinized follicle presented as a minute hemorrhagic cyst on the surface of the left ovary. Microscopically, the cavity was round and spherical and contained free blood. Though not universally present, the cavity presented two to seven layers of true lutein cells. The cells were large, ovoid or round, with clear cytoplasm, and a central nucleus. The theca externa, composed of eight or nine layers of smaller cells, was well differentiated. Huge capillary sinusoids coursed concentrically between granulosa and theca interna. The small round cavity contrasted with the large lining lutein cells. Certainly, rupture of the follicle and normal corpus luteum forma-

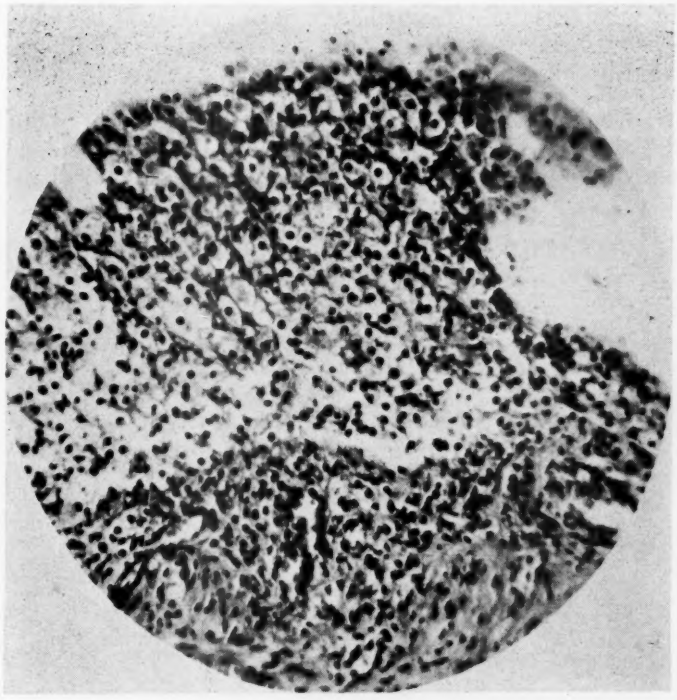

Fig. 3.—Case 5, right ovary. Recent follicular cyst. Hypertrophy of the granulosa cells due to early lipoid deposition. Theca interna cells not prominent.

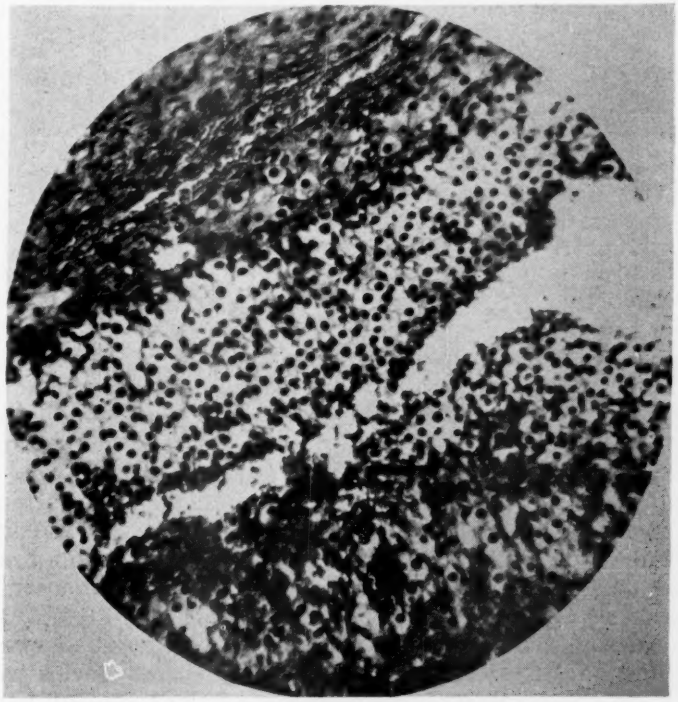

Fig. 4.—Case 11, left ovary. Advanced pseudoluteinization of granulosa cells in a maturing follicle of the current cycle. Nuclei irregular and pyknotic. Theca interna cells more prominent and surround the vessels.

tion cannot be substantiated. This change is unusual and has not been noted by other investigators. It resembles luteinized unruptured follicles of the rabbit ovary stimulated by chorionic gonadotropin.

Follicular Cysts.—Except in old follicle cysts with atrophic cells, the granulosa-cell column and the underlying theca showed decided morphologic changes. Grossly, the cysts were larger and more prominent than normal, often

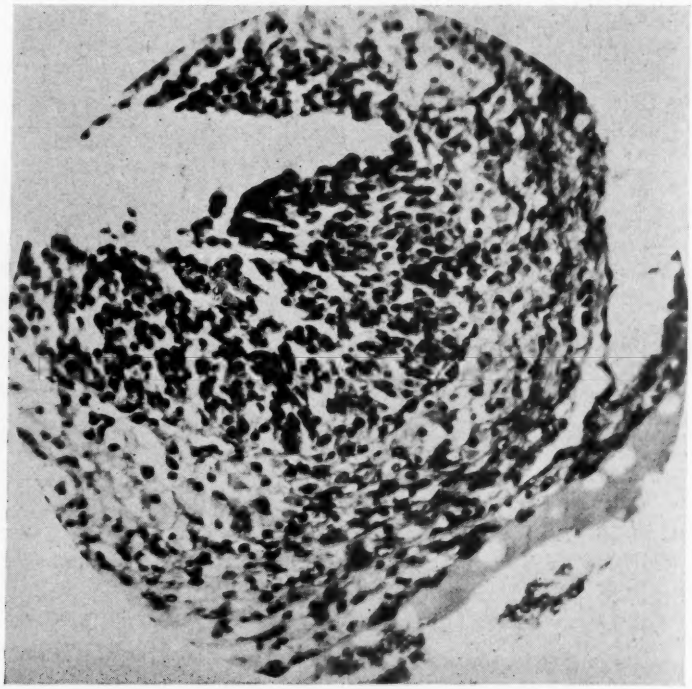

Fig. 5.—Case 14, right ovary. An early corpus luteum of congestion. Note that the lutein cells are not clear and ovoid as above. They are elongated, small, granular and deeply staining.

reaching to 15 to 20 mm. in diameter, with a range from 2 to 25 mm. (Fig. 7). The grossly hemorrhagic appearance has been previously noted. True blood in the cavity was found in four instances. An increased number of follicular cysts could not be established, for there are no criteria even in normal ovaries. Microscopically, the number of cell layers in the granulosa column was seemingly dependent upon the age of the cystic follicle. Yet strikingly irrespective of age, all granulosa cells were larger than normal with a definable amount of pink-staining cytoplasm (Fig. 8). No distinct nuclear changes were apparent, although staining intensity was often slightly increased. As already described, in the most recent follicles, the round central cavity was replaced by a compressed dentate type lined by a serpiginous epithelial column of granulosa cells. Lipoid deposition in the cell body caused marked enlargement of the cell and clarity of its cytoplasm, thus simulating the lutein type. Such follicle cysts are designated as the "pseudoluteinized" type and were encountered in Cases 11 and 15. (See Figs. 3 and 4.) All such follicles were in ovaries injected between the ninth and sixteenth day of the cycle and lipoidization and enlargement of the cells is interpreted as a Gonadogen effect on the granulosa cells of a maturing but unruptured follicle.

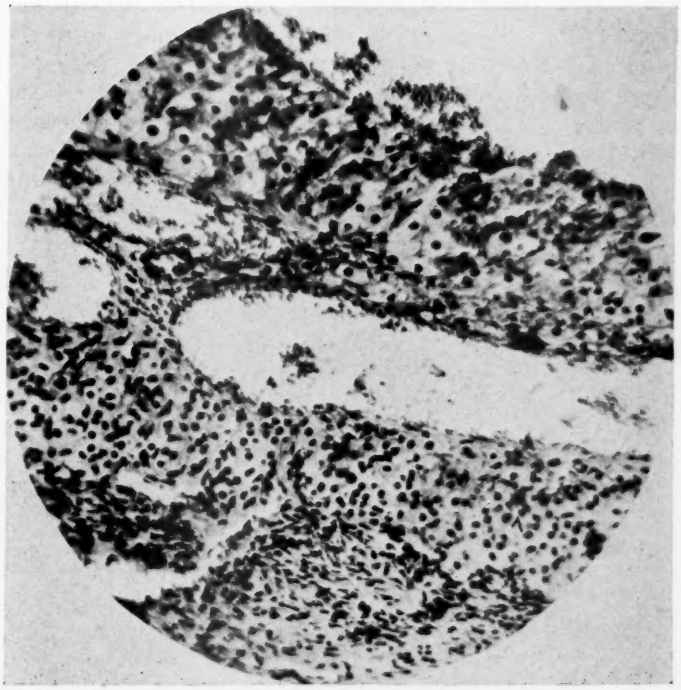

Fig. 6.—Case 1, left ovary. True luteinization of an unruptured follicle. Huge sinusoids underlie the lutein column followed by the broad theca interna zone. The latter cells are smaller and clearer.

Fig. 7.—Case 20, right ovary. Note the double corpus luteum of the same developmental age. The follicular cysts at the periphery are large and prominent. The central one shows marked perifollicular hemorrhage.

Theca Interna.—Changes induced by Gonadogen were most prominent in the theca interna cells. Follicles in every development and regressive stage showed such effects. Even in corpora fibrosa, clusters, islands, or palisaded columns of theca cells were demarcated and surrounded by cellular stroma (Fig. 9). Occasional too solid islands of hypertrophied theca cells were observed, as often seen in an ovary at the end of a normal pregnancy. The large clear cell, its sharp outline, and its central nucleus were prominent. In fairly recent follicles, theca-cell hypertrophy was so pronounced that at times only the presence of the overlying granulosa permitted true recognition (Fig. 10).

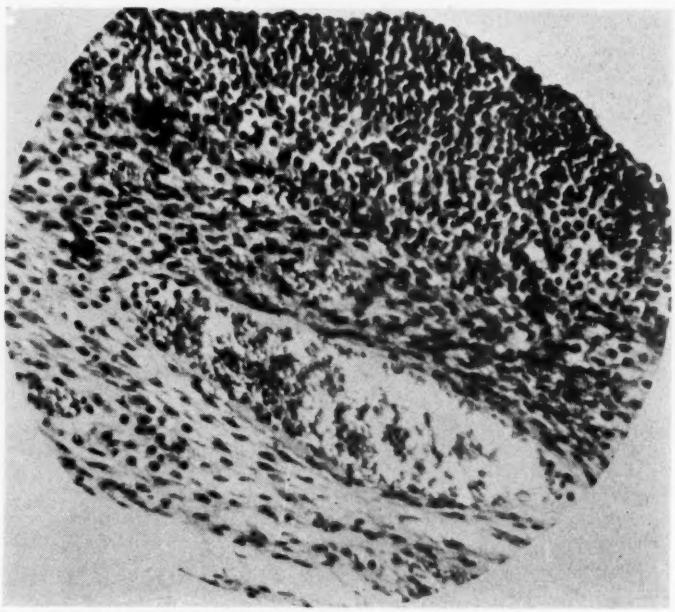

Fig. 8.—Case 15, right ovary. Early pseudoluteinization of the granulosa in a currently maturing follicle. Note the clarity of the granulosa cells near the theca interna. The theca interna cells show mutation from the spindle to the epithelioid to the ovoid form.

Such theca interna cysts could be told in the gross by their smooth, thin, yellow-tinted lining, and were encountered in 9 of 22 cases in this series. In older degenerated follicle cysts, the fibrous tissue mantle separating the hypertrophied theca-cell column from the cavity indicated reactivation of old theca cells. The number of adjacent capillaries was not increased but they were, however, often congested.

Corpora Lutea.—These were encountered in 14 cases as follows: corpus luteum of congestion, 4 cases; corpus luteum of vascularization, 5 cases; corpus luteum of efflorescence, 5 cases. All presented the morphology typical of their cyclic stages and corresponded to corpora of the current cycle. Multiple corpora lutea were frequent but were always of the same developmental age and form (Fig. 7). There were two instances of bilateral corpora lutea and three cases of multiple corpora in the same ovary. These findings are explained by hyperemia due to pressure stasis from the associated fibroids of the uterus. Geist, et al., also noted a high incidence of multiple corpora in their studies with chorionic gonadotropin.

Discussion

There are many clinical and experimental difficulties met in studies of equine gonadotropin. Since most patients in all series had fibromyomas of the

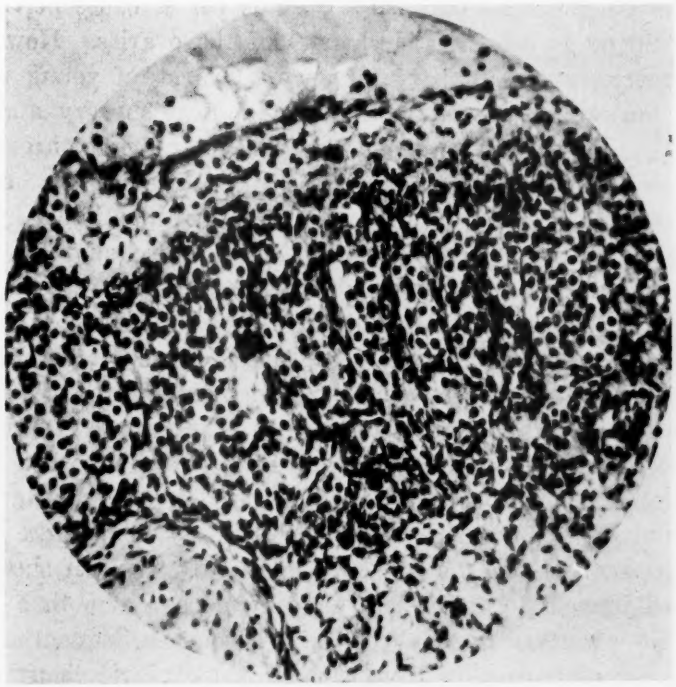

Fig. 9.—Case 8, left ovary. Theca interna cyst. Hypertrophy of the theca cells is pronounced. They are palisaded in columns defined by fibrous septa. The degenerating granulosa cells centrally line the cavity.

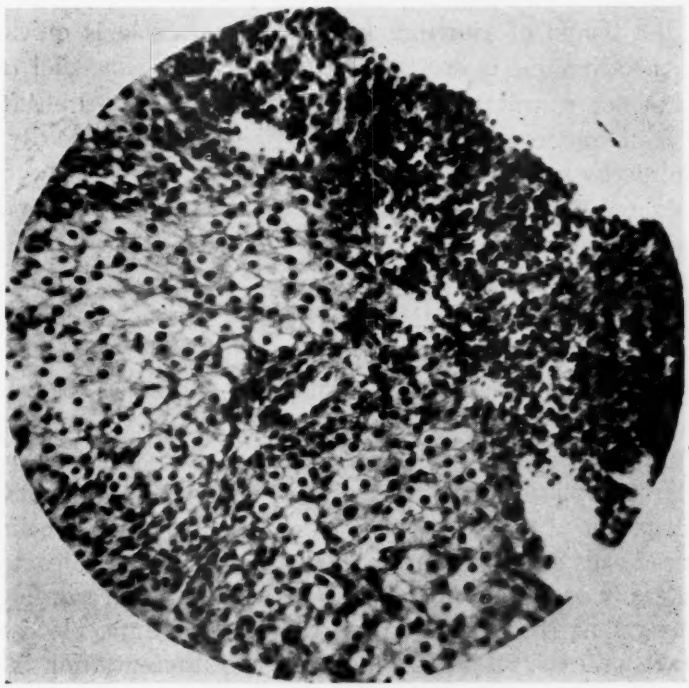

Fig. 10.—Case 15, left ovary. Hypertrophy of the theca interna in a recent follicle is most marked. Only the overlying granulosa layer differentiates theca cells from the true lutein type.

uterus, it must be indicated that large fibroids per se cause pelvic congestion, ultimately resulting in sclerocystic changes of the ovaries. How such organs respond to experimental stimuli is unknown. Ovaries of young women would appear most desirable for examination, yet radical surgery and removal of organs can only be practiced upon older patients. It is not unreasonable, however, to assume that gonads which ovulate and produce corpora lutea should be functionally receptive and morphologically responsive to stimulation by gonadotropic agents. Objections on an age basis, therefore, are not valid. The time of the cycle during which Gonadogen is given is of importance, for cyclic ovarian changes are occurring concurrently with those which may be induced by Gonadogen. Thus, in the midcycle, a recently ruptured follicle may be falsely ascribed to equine gonadotropin, and reversely, the actual rupture induced by use of this agent may be wrongly interpreted as normal to the cycle. The time factor becomes even more pertinent in the third week of the cycle when estrogen and progesterone secreted by the normal corpus inhibit the pituitary gland. A physiologic anatogonist, therefore, is present which can interfere with stimulation by Gonadogen. In retrospect, studies with Gonadogen should have best been conducted immediately after the close of menses, at a time when normal inhibition to the pituitary by estrogen is in abeyance. Sequential observations are necessary for evaluation of functional or morphologic changes induced by Gonadogen but are not available in any plan of study presented to date. Positive proof of ovarian stimulation by gonadotropins requires evidence that more than the usual number of Graafian follicles are brought to maturation and ovulation or that the tempo of ripening in a solitary follicle is quickened. Basic knowledge in this direction is scant, for the number of primordial follicles which normally commence simultaneous maturation is not known. After ovulation has occurred from one, ova from contemporary follicles supposedly disintegrate. How long the discus proligerus surrounding such a degenerating ovum persists before the blighted follicle undergoes cystic atresia is not known. How then can the atresic follicle of the current cycle be distinguished from a persisting cystic follicle of the antecedent period?

In addition, the "pseudoluteinized" follicles of the current cycle (Figs. 3 and 4) which result from Gonadogen stimulation can be mistaken for a recently ruptured follicle with incipient corpus formation. However, the collapsed cavity of the normally ruptured follicle is more dentate, and a "punktum" is grossly observed. The early lutein cells, as already noted, are small, with scant acidophilic granular cytoplasm. The nucleus is small, round, and dark. The next change is elongation of the cell body, which later assumes a cylindrical form. Clear vacuolated cells are not seen until vascularization of the corpus is reached. This phase is easily identified in the gross by the large, measurable corpus presenting a gray-yellow lining enclosing a central coagulum, blood-tinged at the point of contact with the lutein cells. Once such differentiation is made, ovulation resulting from Gonadogen stimulation is excluded with certainty. In our study, ovulation was not established.

Conclusions

1. Experiments with equine gonadotropin (Gonadogen) as conducted in the human being are beset with numerous conflicting conditions, and binding conclusions are hardly warranted.

2. Such studies are best made in the immediate postmenstrual period when spontaneous maturation and ovulation have hardly begun.

3. Gonadogen does not cause orderly maturation of unusual numbers of Graafian follicles nor does it accelerate the tempo of maturation in follicles of a current cycle.

4. Although the primordial follicular unit is not stimulated, the granulosa layer is hypertrophic, due to increase in cell cytoplasm. In granulosa cells of a current follicle, the size and clarity of the cell simulate the lutein type and the term "pseudo luteinization" is warranted.

5. Hypertrophy and hyperplasia of the theca interna layer is the most marked Gonadogen effect. Reactivation in atresic follicles and even in corpora fibrosa occurs. Theca interna cysts are numerous.

6. Vascular engorgement is prominent and accounts for the hypertrophy of the granulosa and theca interna cells. Interstitial and intrafollicular bleeding is in frequent association.

7. The position of Gonadogen in the therapy of amenorrhea still remains problematic. It stimulates the granulosa and theca components of the maturing follicle or follicle cysts. There is no proof of inauguration of follicle maturation or rupture, induced by equine gonadotropin.

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CHOREA GRAVIDARUM

Review of the Recent Literature and Report of Five Cases

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CHOREA gravidarum is an infrequent complication of pregnancy. Beck,[1] however, warned that though rarely observed it occasionally presents a grave problem. Ruch[2] suggested that the clinical picture which it presents is perhaps the most distressing of all the complications which the obstetrician encounters. The infrequent occurrence of this condition and the ominous portent which the diagnosis may convey warrant the presentation of five previously unreported cases. Moreover, to our knowledge, a consideration of the literature relevant to this problem has not been attempted since the monumental review of the subject by Willson and Preece[3] in 1932. We have prepared a list of references of the articles which have appeared on this subject since that date and will consider briefly the conclusions of the American reports and of those available from the foreign literature.

Willson and Preece's article contained approximately 330 references from the world's literature to Sept. 30, 1930, and they submitted questionnaires to 530 members of obstetric societies throughout the United States inquiring whether or not these members had ever encountered this condition. From these data, the authors assembled with meticulous detail information concerning 951 choreic pregnancies occurring in 797 patients. A brief summary of the essential material from their communication will be presented. These data will serve as a convenient point of departure from which to consider the subsequent literature.

Survey of the Literature

Data from thirteen American hospitals suggested a hospital incidence of 1 case per 3,501 obstetric admissions. Extremes in incidence were 1 case of chorea among 146 pregnancies reported by Scott from Toronto and no case in 20,000 deliveries at the Dublin Rotunda. Willson and Preece suggested that the incidence in American hospitals gave an exaggerated concept of the frequency of this complication, since of 170 obstetricians replying to their questionnaire, 113 had never observed a case.

The average age of the patients was 22.4 years. Chorea associated with pregnancy was observed much more frequently in primigravid patients. An illegitimacy rate of 17.2 per cent was observed. The authors commented on the rarity of this complication in the Negro race.

A history of chorea unassociated with pregnancy was given by 48.1 per cent of the patients, and 12.8 per cent gave a history of chorea, the relationship of which to pregnancy was undetermined. Occurrence of previous episodes of chorea was denied by 39 per cent. A history of rheumatism was given by 35.3 per cent. Heart disease was noted in approximately one-third of the 797 patients. In approximately two-thirds of the pregnancies, there was a history of chorea or rheumatism or both. In sixty-eight cases of their series, some form of emotional disturbance preceded the attack. Pathologic data were admittedly incomplete, but of the forty-six cases in which necropsy was performed, cardiac pathologic change was observed in 86.9 per cent. Evidence of low-grade encephalitis was noted in some cases. Several investigators reported finding congestion and petechial hemorrhage and thrombosis in almost every part of the brain, such processes reaching a quantitative and qualitative maximum in the corpus striatum, especially in the caudate nucleus. The pathologic evidence as summarized in 1932 lent no support to the opinion that the toxemias of pregnancy have any etiological relationship to chorea gravidarum.

Half of the attacks were initiated in the first trimester, and a third in the second, and a sixth in the third trimester. In 529 pregnancies with nonfatal termination, the chorea ceased ante partum in 167, intra partum in one, and post partum in 361. In cases in which the patient died during pregnancy, the disease tended to run a shorter course. The average duration of those attacks terminating in recovery during pregnancy was about two and a half months.

The well-known symptom complex consists chiefly of hypermotility and incoordination, usually generalized. The movements usually cease during sleep. The patients are usually afebrile, and when fever does occur it is of ominous significance. Hyperpyrexia can occur.

The most frequent complications were stated to be acute psychosis, acute endocarditis, and rheumatic fever. Eclampsia occurred in six cases, in three cases chorea was complicated by hysteria, and in one, by epilepsy.

Encephalitis, pseudochorea, and pseudosclerosis were noted as entities to be considered in the differential diagnosis. Prior to the publication of Willson and Preece, mortality rates had run between 25 and 33 per cent. It was stated by these authors to be about 12.7 per cent from 1900 to 1932 in what they termed the "aseptic era in obstetrics," to differentiate this period from previous time intervals. A lower mortality rate was noted in cases of patients who had had chorea or rheumatism previously, and a still lower rate in those who had had both. Mortality rate appeared to have no relation to the month of pregnancy at onset. In cases in which spontaneous labor occurred at term, a mortality rate of 1.9 per cent was reported; in cases in which spontaneous premature labor occurred, 12.6 per cent; and in those in which spontaneous abortion occurred, 23 per cent. In a group of 171 cases in which pregnancy was terminated artificially, a mortality rate of 33.3 per cent was found.

The authors warned against the excessive use of depressant drugs. Sedation, adequate nourishment, rest, and general supportive measures were the common denominators of successful management. In cases of mild chorea, no reason for therapeutic abortion could be found. If intervention need be resorted to, Willson and Preece advised that the cases be selected carefully and that such interruption be by the induction of premature labor or abortion and not by immediate operative delivery except in rare instances, as the mortality rate for such procedures was about 50 per cent. The most reasonable indication for interference seemed to be progression of the chorea despite therapy, and they felt interruption should be carried out before infection occurs.

We were able to find thirty-three articles concerning chorea gravidarum from 1932 through December, 1946. A résumé of those available to us follows.

Guynes[4] reported a case of fatal chorea gravidarum which developed in one week's time in the ninth month of gestation. The patient was a Mexican woman in her second pregnancy. The patient gave a history of mild chorea in the first pregnancy which was terminated by premature labor. In the pregnancy under consideration, labor and delivery were hastened by manual dilatation when the cervix was dilated to a diameter of about 5 cm. This procedure was resorted to because of the extremely serious condition of the patient. Cesarean section previously had been refused. Hyperpyrexia developed and the patient died on the second postpartum day. The authors concluded that it did not seem wise to temporize even in cases of apparently mild chorea complicating pregnancy in the later months. Hysteria, tic or habit spasm, epidemic encephalitis, senile chorea, Huntington's chorea, Friedreich's ataxia, and various intoxications were mentioned as entities to be considered in the differential diagnosis.

Kobrinsky[5] presented a case of a 19-year-old, unmarried primipara who presented no evidence of cardiac disease. Chorea gravidarum developed in the sixth month of pregnancy and distinct improvement followed transfusion of 20 c.c. of blood from a healthy, pregnant woman. The author considered the chorea in his case to be of toxemic origin, as examination of the patient's urine showed heavy traces of albumin and granular casts, and edema of the ankles had been noted. The pregnancy was concluded in the eighth month after medical induction of labor. A normal female infant was born.

Brian and Gerundo[6] reported a case in which they felt chorea was related to toxemia because of the nephrohepatic lesions found at necropsy. This patient, a secundigravida 35 years old, had not had albuminuria, edema, or hypertension in the prenatal period, as far as was known. The heart was normal. The patient was thought to have had acute cholecystic disease with icterus, a septic fever, and some vomiting in the fourth month of pregnancy. The authors in retrospect concluded that this might have been an episode of parenchymatous hepatitis. The chorea apparently began about one month before delivery. The patient was delivered of a dead fetus in what was probably the seventh month of gestation and died one month after delivery. The authors felt that the clinical course and the nephrohepatic lesions in this case could serve to distinguish chorea of rheumatic origin from that of toxemic origin. They felt that because hepatitis and possible pre-eclampsia preceded the chorea it was also of toxemic origin.

Weigner[7] submitted a strong brief for the psychogenic origin of certain instances of gravidic chorea. In defense of this viewpoint he presented the following data: In 17 per cent of the cases the pregnancy was illegitimate. He stated that the peak occurrence was in the fifth month of gestation when quickening and other positive signs of pregnancy removed all doubt from the patient's mind as to the interpretation of the unwanted amenorrhea. He pointed out the fact that many cases have considerable psychogenic "color" and that patients in these cases were often cured by abortion or by dramatic and obviously nonspecific therapy such as sham abortion, cervical dilatation, incision of the hymen for the relief of dyspareunia or the removal of a urethral caruncle. Seventy cases from the literature were noted in which there were precipitating instances of an emotionally shocking nature such as fright, anger, a fall, or fire. Of 950 cases in the literature, some evidence of psychogenesis was mentioned in 137. In this particular group, the rheumatic background was mentioned in significantly fewer cases than in the cases in which evidence of psychogenesis was lacking. Weigner's conclusion was that chorea gravidarum should not be regarded as an entity but instead as an expression of a constitutional anlage which may be precipitated by various factors such as infection, toxemia, or psychogenic stimulation. The work of Gerty was mentioned. A report of a remarkable case was presented in which a striking psychogenic com-

ponent was evident. The chorea was terminated by suggesting in the presence of the patient that the pregnancy could be terminated were she to improve enough for such a procedure to be carried out. This patient previously had had chorea associated with tonsillitis. Development of chorea in response to both infection and psychogenic stimuli strengthened the ultimate conclusion that this phenomenon was a manifestation of a constitutional anlage. The term "choreiform behavior in pregnancy" was suggested as more precise than "chorea gravidarum."

Scheftel[8] reviewed the literature to some extent and described the various hypotheses of etiology. She presented a case of a hysterical, mentally retarded woman who had hemichorea in her first pregnancy and presented a double mitral lesion. In the second pregnancy, chorea of a mild type recurred. In a third pregnancy, the chorea was generalized and moderately severe. The offspring had atypical Klippel-Feil syndrome.

Patterson[9] reported a case of severe chorea in an unmarried girl, which he felt had been induced by the worry and shame caused by the pregnancy. Sodium Amytal appeared to have a definite beneficial effect but the bromides and morphine sulfate appeared to be of little value. Real improvement, however, did not occur until the pregnancy was terminated artificially. The past history was not given. No cardiac lesion was found. The temperature was normal. Surgical induction of labor was carried out at thirty-four weeks and the premature infant died fourteen hours after delivery.

Ruch[2] summarized many of the salient points of the recent literature and referred to chorea gravidarum as a rare disease. He reported a single case. The patient was the wife of a medical student. Chorea developed in the fourth month of gestation. No clinical history of rheumatic fever was obtained nor was there a demonstrable cardiac lesion. However, intermittent low-grade fever was present and a polyarthritic episode occurred after therapeutic emptying of the uterus by cesarean section in the sixth month. Ruch quoted Royston to the effect that if a choreic patient becomes pregnant the prognosis is not necessarily serious, whereas if chorea appears for the first time after conception, it is always of grave import and failure to distinguish between these two situations probably explains the marked variations in mortality figures. DeLee[10] is quoted regarding the occasional cases of chorea associated with fetal abnormalities and the statement was made that such abnormalities often are confined to the head and spinal column. Ruch stated that the left side of the body is more commonly involved and that personality changes often are noted. Involvement may vary from mild twitching in an isolated muscle group to generalized disability causing impairment or total loss of powers of speech and deglutition often necessitating forceful restraint. In the majority of cases the chorea is mild. In cases of severe chorea, Ruch advised termination of pregnancy—the sooner done the better—and stated that delay invites a higher mortality. Abortion is regarded as the procedure of choice, although cesarean section is usually preferable if the pregnancy is well advanced and the choreiform movements become violent. Fever is listed as an added indication for intervention.

The foreign literature, like the English literature, has consisted mostly of reports of single cases.

Dražančić[11] emphasized his mode of treatment of a primipara in the fifth month of pregnancy. The patient was given twelve subcutaneous injections of peptone and improved after the first treatment. The author was of the opinion that he was the first to have attempted this form of treatment. The patient lived and the child died of unknown cause on the sixth postnatal day. The author concluded that chorea associated with pregnancy was neither neurogenic

nor infectious but was allergic in origin. He felt that the allergenic factor might be a protein stemming from the fetus and hence used the peptone as a desensitizing agent.

Nordmeyer[12] favored a toxic etiology as most likely in severe chorea gravidarum and reported a case in which a definite rheumatic background, cardiac signs, albuminuria, and normal blood pressure were noted. He obtained a favorable result with cesarean section and stated that this procedure should be carried out when the condition is severe.

Thiele[13, 14] reported twenty-one cases which had been encountered in twenty years with one death. Döderlein[15] reported seven cases.

Levy-Valensi and his colleagues[16, 17] presented a case in which evidence of toxemia was not found and a previous history of chorea was obtained. The patient died as the result of rheumatic endocarditis. These authors were particularly interested in the concentration of lactic acid in the blood, and on the day of their patient's death the concentration was the greatest they had ever encountered. They postulated that the chorea plus the cardiac decompensation in their case might have produced such a level.

Laffont and Castanier[18] had a secundigravida patient whose first child had had hydrocephalus. Chorea gravidarum developed during the second pregnancy and the patient died. A sister had died of a postpartum psychosis. Their patient had a normal blood pressure and no albuminuria. Necropsy was not performed.

Brémond[19] described a case of chorea in a primiparous patient who was delivered of a normal baby. The patient had received conservative therapy. She had severe vomiting associated with the pregnancy.

Gosende and Sandiano[20] reported a case in which they believed the chorea to have been caused by "the toxins of pregnancy." Dutra[21] and Rabin and Duek[22] described three cases in which cure was effected by pyridoxine (Vitamin B_6) therapy.

Review of the discussions concerning chorea gravidarum in modern textbooks on obstetrics provided the following:

Titus[23] recommended the use of barbiturates in moderately large doses. He also suggested the removal of foci of infection, keeping the patient at absolute rest in bed, use of a high carbohydrate diet, and the parenteral administration of a hypertonic solution of glucose to compensate for excessive glycogen consumption by constantly jerking muscles.

Beck[1] emphasized rest in bed, isolation, careful feeding, and the use of sedative drugs as therapeutic measures. He further suggested that intravenous injection of a solution of magnesium sulfate often has a quieting effect when other sedatives fail. Improvement after the use of arsphenamine has been noted.

Irving[24] emphasized the seriousness of prognosis if chorea occurs for the first time during pregnancy and gave the mortality rate as 18 per cent. If it occurred in a previous pregnancy, the rate is about 10 per cent and if the chorea of pregnancy represents a recrudescence of adolescent chorea the mortality rate is about 7 per cent. He stated that about 25 per cent of women who have chorea during adolescence have a recurrence during pregnancy. In the presence of fever, the mortality rate is said to be about 70 per cent.

Stander[25] quoted Wilson whose opinion was that induction of abortion is unnecessary in cases of mild chorea and does no good when the condition is severe. Twelve cases in 34,569 pregnancies were encountered at New York Lying-In Hospital.

Mengert[26] mentioned an insidious onset, a course of from eight to ten weeks, with recovery the rule. He suggested rest in bed, quiet, seclusion, good hygiene, and sedatives, such as phenobarbital, paraldehyde, and choral hydrate, when the movements become too severe.

Previous editions of DeLee's[10] text stated that incontinence of urine and feces is a bad omen and that jaundice is regarded similarly. He gave the duration of chorea gravidarum to be from eight days to eight months. The fact that the offspring might be choreic was pointed out. It was stated that permanent mental disturbances in the mother may follow. In a discussion of treatment, isolation in a dark, quiet room, the giving of a vegetable and fruit diet (rich in vitamins, especially B) and abundant fluid was suggested. The physician was urged against temporizing. When hypocalcemia occurs, administration of calcium gluconate and vitamin D was recommended. Treatment with normal pregnancy serum should be tried. It was advised that pregnancy be terminated when general health has begun to suffer, certainly long before incontinence, jaundice, fever, or delirium begins.

Many of these contentions and suggestions are absent from the most recent edition which lists maternal mortality rate varying from 6 to 36 per cent and fetal mortality rate from 50 to 70 per cent. The prophylaxis of chorea gravidarum consists of proper prenatal care. The treatment consists of keeping the patient at rest in bed and administration of sedatives. Emptying of the uterus should be considered if the patient's condition becomes progressively worse. Local anesthesia should be used whenever possible and a neurologist always should be consulted.

Report of Five Cases

From 1922 to 1947, 12,776 confinements were conducted in the obstetric department of St. Marys Hospital. No case of chorea gravidarum was observed. Five cases, however, have been studied at the Mayo Clinic. One of the patients was hospitalized and was treated by us on the emergency gynecology service. The first case to be presented was encountered by us and the remaining four cases were studied by means of clinic records and follow-up letters. None of the patients was delivered at the clinic.

Case 1.—A 19-year-old married primigravida was admitted to the clinic and was hospitalized on March 27, 1946. She complained of irregular and uncontrolled generalized movements, persistent vomiting, and loss of weight. The patient had married in September, 1945, and she first missed a menstrual period in November, 1945. She had an irregular three-day period of heavy flow at the midinterval between the September and October periods and a physician elsewhere had entertained a diagnosis of "inflamed ovaries." The diagnosis of pregnancy was presumed with the onset of amenorrhea for the menses had always been regular. Nausea and vomiting began the first part of December and continued until admission. Sore breasts and urinary frequency were noted in January, 1946. Three weeks before admission, the patient experienced some vague, cramplike pains in the lower part of the abdomen which lasted for from a few seconds to several minutes. She was thought to be aborting. At that time she was vomiting on the average of four times per day. Ten days before admission, choreiform movements were noted. The patient first noted some blurring of vision and an inability to hold and manipulate objects with precision. She "wiggled in her chair" and was called "hysterical" by her father. She had no convulsions. She had been admitted to a hospital elsewhere for study and the presumptive diagnosis was toxemia of pregnancy. Edema, albuminuria, or

hypertension was not present at any time. In the two weeks preceding admission to our care, the patient experienced some ten episodes of fairly severe epistaxis, lasting for from thirty to sixty minutes. No history of arthritis, erythema marginatum, subcutaneous nodules, pleurisy, sunlight intolerance, or headache was given.

The patient had scarlet fever at the age of 13 years and following this had chorea which lasted for four months. She did not have arthritis and was not told of any cardiac complication. Two weeks after recovering from the chorea, the patient had "brain fever" with paralysis of her right arm and leg which lasted only a few days. She was unconscious for this period and her parents "despaired of her life." The present episode of chorea was the first since the childhood attack. The family history was noncontributory.

On admission to the hospital, the patient was unable to stand, to feed herself, or to talk intelligibly. The temperature was 98.0° F.; the pulse rate, 76 beats per minute; the respiratory rate, 20; and the blood pressure, 116/54. The patient appeared to be dehydrated and evidence of loss of weight was observed. The patient had lost 40 pounds (18.1 kg.) after she became pregnant. The choreiform movements were noted and thought to be of grade 2 intensity (on a basis of 1 to 4 in which 1 represents the least and 4 the greatest intensity). Scattered, nonelevated, erythematous blotches, 2 to 3 cm. in diameter, were observed on the cheeks, arms, and legs.

Results of examination of the optical fields and fundi were negative. Evidence of previous choroiditis was noted. Negative results were obtained on neurologic examination. It was impossible to perform the Romberg test and gait was not observed.

Slight cardiac enlargement, absence of thrills, and regularity of rhythm were noted. Presystolic and systolic murmurs were noted at the apex and a diastolic murmur was noted to the left of the sternum in the third interspace. No evidence of decompensation was discernible.

The size of the uterus suggested a gestation of five months. The fetus was active and the fetal heart, audible. An additional history of slight vaginal bleeding two weeks before admission was obtained.

Results of laboratory studies are given in Table I.

The diagnoses were chorea gravidarum, hyperemesis gravidarum, active rheumatic fever, chronic rheumatic endocarditis with aortic insufficiency, and mitral stenosis and insufficiency.

While the patient was in the hospital, the respiratory rate was never more than 20, the pulse rate never more than 80, and the temperature was never above 98.6° F. except on the day of admission when it was 99.6° F. The blood pressure was 116/54 on admission of the patient, and subsequent determinations were approximately the same. The patient was hospitalized for nineteen days.

The treatment offered was essentially supportive: 2,000 to 3,000 c.c. of a solution of dextrose (1 liter only containing saline) was given intravenously daily for five days with 100 mg. of ascorbic acid (vitamin C), 50 mg. of pyridoxine (vitamin B_6), and 1 ampule of additional supplementary vitamin B added to the fluid. A minimum of visitors was allowed to see the patient. The room was darkened and kept quiet. Two grains (0.13 Gm.) of phenobarbital sodium was given hypodermically twice a day and 1½ grains (0.1 Gm.) of phenobarbital was given by mouth twice a day. Later Nembutal (pentobarbital sodium) and belladonna capsules were given.

TABLE I. LABORATORY STUDIES OF CASE 1

	RESULTS
Urine	Specific gravity: 1.005 to 1.017
	Alkaline
	No sugar, albumin, acetone, or diacetic acid
	Occasional pus cells in uncatheterized specimen
Blood	Hemoglobin: 13.6 and 12.2 Gm. per 100 c.c.
	Erythrocytes: 4,280,000; 4,090,000 per cubic millimeter
	Leucocytes: March 28, 9,500; March 30, 6,300; April 4, 7,300; May 6, 12,400 (two readings) per cubic millimeter
	Differential count: 43 per cent, immature polymorphonuclear leucocytes; 40 per cent mature forms; 12 per cent lymphocytes; 5 per cent monocytes
	Urea: 22 mg. per 100 c.c.
	Chlorides: 583 mg. per 100 c.c. of plasma
	Carbon dioxide combining power: 48.5 volumes per 100 c.c. of plasma
	Serum calcium: 9.5 and 8.2 mg. per 100 c.c. on two successive days
	Serum protein: 7.4 mg. per 100 c.c.
	Flocculation test: negative
	Sedimentation rate (Westergren): March 27, 63 mm.; March 30, 51 mm.; April 3, 67 mm.; April 13, 61 mm. in one hour
	Culture (brain broth and blood agar): no growth in 48 hours
Roentgenologic examination	Elevation of the left side of the diaphragm
Electrocardiographic examination	Heart rate, 85; sinus arrhythmia; T_3 of low amplitude; P_2 and P_3

Slight improvement was noted on the third hospital day both in the course of the vomiting and chorea. The patient vomited four times on the first day of hospitalization, three times on the second day, and only once on the third day. By the fifth day definite improvement was observed, and frequent light, dry feedings were offered. On the seventh hospital day, a general diet was allowed and the choreiform movements were then difficult to detect. Pyridoxine was given by mouth for five days thereafter in 50 mg. doses.

Beginning on the twelfth hospital day, 20 grains (1.3 Gm.) of sodium salicylate were administered in enteric-coated tablets three times a day and 4 mg. of vitamin K was given each day. Supplementary vitamins, especially those of the B complex and iron were taken by the patient. She was discharged on the nineteenth hospital day and was advised to return at intervals.

She returned on May 6, 1946, feeling well. The sedimentation rate was 54 mm. (Westergren). The pulse rate both at rest and after exercise was elevated only slightly. Administration of the salicylates was continued. On June 3, 1946, all medication except iron and vitamin supplements was discontinued. The patient felt well. The sedimentation rate was still elevated (62 mm.). On June 15, when the patient was examined elsewhere, albuminuria was graded 1+ and the ankles were slightly swollen. The albuminuria and swelling subsided when she stayed in bed for a few days. Determination of the concentration of salicylates in the blood was carried out on three occasions during our observation of this patient. The results were: April 10, 1946, 10.4 mg.; May 6, 1946, 20.2 mg.; June 3, 1946, 4.2 mg. per 100 c.c.

The patient was delivered of a normal female infant weighing 5 pounds (2.3 kg.) by her local physician on July 8, 1946. The postpartum period was uneventful for both mother and infant.

CASE 2.—A 25-year-old woman, gravida iii, para ii, registered at the clinic July 20, 1925, in the fifth month of pregnancy. Her chief complaint was of choreiform movements. Study of the family history revealed that the father had died of diabetes and one brother had "sick headaches." The patient had had influenza, scarlet fever, and tonsillitis as a child. She had had rheumatic fever seven years before admission and chorea six years before admission and had undergone tonsillectomy five and a half years before admission. The patient had had headaches since the age of 12 years, had blurred vision at times, and had diminished hearing with tinnitus on the right side. The menses had always been normal. The patient had worked as a seamstress from the age of 18 years and enjoyed her work except that when she was very busy she became extremely nervous. Her mother became ill seven years before the patient came to the clinic and the patient carried on the work of sewing for both of them. She suffered a "nervous breakdown" and had "exaggerated choreiform" movements the first time for two and a half weeks and it was necessary for her to stay in bed. She recovered slowly and underwent tonsillectomy during her convalescence. She married because she was told that marriage and pregnancy would improve her nervous condition and that if she did not marry she would probably become worse.

Four years before admission, after three months of marriage, she became pregnant and began to have choreiform movements so severely that she could not hold things in her hands or speak. Associated symptoms were blurring of vision, a "sickening feeling in the bones" of her arms and legs—akin to weakness and numbness—and pain in the back. The chorea subsided in the fifth month of gestation after one month of hospitalization and the remainder of the pregnancy was uneventful.

She suffered chorea in the first half of the second pregnancy, one and a half years before admission, with the same associated symptoms, which cleared in the second half of the pregnancy. She was then well and had never felt better until five months before admission when she became pregnant again and the chorea returned.

On admission she was unable to keep her arms or her legs still and was described as being very fidgety. The speech was not articulate and facial grimacing was present. She suffered some shortness of breath and felt as though the movements of her chest were restricted. Additional complaints were of urinary frequency, nocturia, back pain, and loss of 11 pounds (5.0 kg.).

On physical examination the temperature was 99.4° F.; pulse rate, 96; and blood pressure, 140/85. The teeth were in poor condition. Examination of the heart revealed a faint, diastolic murmur at the base. The size of the uterus was consistent with a five-month gestation.

Examination of a noncatheterized urine specimen revealed albuminuria, grade 2 plus, and pyuria, grade 1 plus. Erythrocyte count was 3,560,000 and leucocyte count, 9,300 per cubic millimeter, and the concentration of hemoglobin was 56 per cent. The color index was 0.7 plus. Differential count revealed the following: 78 per cent polymorphonuclear neutrophilic leucocytes, 16.5 per cent lymphocytes, 3.5 per cent eosinophiles; moderate anisocytosis, slight poikilocytosis and polychromatophilia. Wassermann test gave negative results.

No abnormalities were found during examination of the eyes, ears, nose, and throat. Neurologic examination gave negative results. In psychiatric interview, the patient confided that coitus had never been pleasurable.

The clinical impression was that chorea gravidarum was present and it was felt that the patient might have low-grade, chronic nephritis on the basis of the albuminuria, elevated systolic blood pressure, and slightly diminished renal function. Routine suggestions for the management of chorea were made. It was advised that renal function be observed carefully for the remainder of the pregnancy. Follow-up letter stated that the patient was delivered of a normal baby without untoward incident.

CASE 3.—A 23-year-old married multipara, gravida iv, para iii, reported to the clinic in March, 1931, in what was thought to be the seventh month of pregnancy. She was referred to the clinic with a tentative diagnosis of brain tumor. One brother had committed suicide. The patient had had scarlet fever, influenza, and tonsillitis as a child. She underwent tonsillectomy at the age of 10 years. The menses had always been normal but the patient always suffered dizziness at the time of her menstrual periods.

Four months before admission, in the third month of pregnancy, the patient noted some weakness in her right arm while playing cards and later some weakness in the right leg. She had difficulty in walking. Subsequently, weakness in the right side of the face and difficulty in talking were noticed. Her words seemed "thick and unmanageable." The patient slept poorly, was nervous, and had much more difficulty when she was being watched. Slight anorexia was present.

In the course of the neurologic examination the patient told that she had had slight tinnitus for fourteen years and complete deafness of the left ear. In the two months preceding admission, the patient had noted slurring of her speech and attacks of dizziness. She had had blurring of vision for one month. It was discovered that the weakness and incoordination of the right arm came on overnight after she saw her mother who was quite ill. The patient was irritable and cried frequently without provocation. She complained that her tongue felt too big for her mouth. She admitted that she worried considerably over her health and that she and her husband had many financial worries. She had been unable to do any work for one month.

Physical examination showed the temperature to be 98.0° F.; the pulse rate, 76; and the blood pressure, 122/70. Obesity, slight pallor, and a seven-month gestation were noted. The patient talked out of the left side of her mouth. Slight facial palsy was observed and was considered to be more apparent than real. She had great difficulty in talking and articulated poorly. Slight horizontal nystagmus was present. The teeth were in fair condition. The abdominal reflexes were absent. Coarse, jerky, uncoordinated, purposeless movements, more marked on the right side, were described by the examiner.

Examination of the heart and lung revealed no abnormalities. Examination of the eyes, including fields and fundi, gave negative results. Active gingivitis was noted in the course of dental examination.

Laboratory examination of a noncatheterized specimen of urine showed albuminuria, grade 2 plus, pyuria, grade 1, and a slight trace of sugar. The erythrocyte count was 4,250,000 and leucocyte count, 9,500 per cubic millimeter, and the concentration of hemoglobin, 14.7 Gm. per 100 c.c. Result of the flocculation test for syphilis was negative. Roentgenograms of the head and thorax did not show any abnormalities.

A diagnosis of chorea gravidarum was made after a diagnosis of early multiple sclerosis had been excluded.

The patient subsequently gave birth to normal twins (a male, 6 pounds [2.7 kg.], and a female, 7 pounds [3.2 kg.]). Two years after this twin pregnancy, the patient gave birth to a normal female child. During this last pregnancy, chorea did not recur. Both deliveries were without untoward event.

CASE 4.—A married unipara, 21 years old, gravida ii, para i, was studied at the clinic in August, 1940, in the fifth month of pregnancy. Her chief complaint was of nervousness. The family history was of no particular significance except for the information that the patient's mother and aunt had both been extremely nervous during their pregnancies but not to the extent that the patient was. Study of the past history showed that the patient had had rheumaic fever at the age of 9 years and mild scarlet fever associated with migratory polyarthritis of six weeks' duration at the age of 18 years. The menstrual history was normal. In September of the preceding year, after two years of marriage, the patient had had a full-term pregnancy and after a long labor was delivered of an infant who weighed 9 pounds (4.1 kg.). She had been discharged from the hospital in seven days.

The patient had apparently been normal until January, 1940. At that time, rheumatic fever developed and she was in bed for a month. Following this episode, she failed to gain strength and lacked ambition. In March, the patient's speech began to become thick and slow and this condition progressed until the middle of June when she could hardly speak at all. The last menstrual period began March 28, 1940. About that time, she had begun to note uncoordinated movements of the head and extremities. She did not "feel nervous." She was hospitalized elsewhere from June 21 to 29, without improvement. She was studied by several physicians and by an osteopath. Treatment had consisted of injections of liver extract. Shortly before the patient's admission, painful areas on the legs and a sore mouth developed. The lesions on the legs appeared in crops. She had noted a tendency to easy bruising. Members of the Department of Neurology obtained some additional information. It was noted that the patient's mother had sick headaches. The patient had had headaches since early girlhood. These had improved after her marriage. The patient had always been emotionally labile.

On physical examination the blood pressure was 100/78, and the pulse rate, 88. The patient was unable to sit still, and movements of the extremities and the head were continuous and purposeless. There was much grimacing. The patient had extreme difficulty in walking, talking, and swallowing. Nystagmus was not noted. Hypertrophy of the tonsils was grade 1. Bilateral submaxillary lymphadenopathy was noted. The lungs were normal. No cardiac abnormality was noted. Ears and nose were examined and found to be normal. Reddened, warm, slightly painful, blue, quarter-sized lesions were observed on the legs. On neurologic examination, grimacing, hypotonia, diminished deep reflexes, and adiadokocinesis were observed. Speech impairment and inability to perform fine movements were also noted. The lesions of the skin were thought to be symptomatic of dermatitis medicamentosa as a history of intake of bromides was obtained. A dental examination revealed no foci of infection.

Examination of the blood showed the concentration of hemoglobin to be 11.0 Gm., an erythrocyte count of 4,100,000, and a leucocyte count of 7,400. Differential count showed 66 per cent polymorphonuclear neutrophilic leucocytes, 26 per cent lymphocytes, 7 per cent monocytes, and 1 per cent eosinophiles. The platelet count was 121,000 per cubic millimeter of blood. Flocculation test for syphilis and roentgenologic examination of the thorax and head gave negative results. The coagulation time was five minutes, clot retraction was complete at one hour, and the sedimentation rate was 45 mm. per hour.

The clinical impression was that chorea gravidarum and dermatitis medicamentosa were present. The patient was advised to rest, take sedatives and vitamin supplements, and to stop taking bromides.

The patient was delivered of a normal infant, January, 1941, elsewhere, without further difficulty. Another baby was born in December, 1945; chorea did not recur.

CASE 5.—An unmarried primigravida, 19 years old, registered at the clinic in January, 1946. Her chief complaints were of nervousness and amenorrhea. The patient wondered if the nervousness represented a recurrence of chorea which she previously had had and if the amenorrhea represented pregnancy which she feared. Her family history was noncontributory. The patient had had chorea at the age of 12 years. She was in bed for a period of three months and was unable to walk or talk and suffered with severe generalized twitching movements. She cried a good deal. Tonsillectomy had been performed in 1941. Menstrual periods always had been irregular, occurring at intervals of three to eight weeks. Her last menstrual period had been in September, 1945.

In the middle of October, 1945, the patient began to have morning nausea and vomiting and noted an accentuation of nervousness which had been rather prominent for the preceding two years. At first the nervousness was simply manifested by such things as nail-biting and insomnia. She then noted that she became more easily excitable and easier to anger. Her speech became slurred and in the two months preceding admission she began to notice jerking movement similar to those that she had suffered when she was a child.

On physical examination, the temperature was 98.2° F.; the pulse rate, 66; and the blood pressure, 120/80. The patient recently had lost 3 pounds (1.4 kg.). She was well developed and well nourished, and the physical examination gave completely negative results except for a systolic murmur at the apex and a definite, but soft, presystolic murmur heard when the patient was in the left, lateral recumbent position. On pelvic examination, the cervix was found to be soft and the uterus enlarged to a size consistent with a two-month gestation.

Questioning by the neurologist revealed the following pertinent facts: The mother of the patient was highly emotional and nervous. At the age of 12 years, shortly after the patient injured the lower part of her back, chorea developed. It was determined that the patient intended to marry the alleged father if their religious differences could be settled. On neurologic examination, no nystagmus was noted. The reflexes were normal and slightly more active on the left side. The jerking movements were confined principally to the arms and legs although the face was involved to a considerable extent.

Laboratory study of the urine gave negative results. The concentration of hemoglobin was 13.1 Gm. per 100 c.c. The erythrocyte count was 4,790,000 and the leucocyte count was 7,600. The differential count showed 77.5 per cent polymorphonuclear neutrophilic leucocytes, 15.5 per cent lymphocytes, 4.5 per cent monocytes, 1.5 per cent eosinophiles, and 1 per cent basophiles. The result of the flocculation test for syphilis was negative. Roentgenologic examination of the thorax gave negative results. The electrocardiogram showed a cardiac rate of 72 beats per minute, slight sinus arrhythmia, and slurred QRS I and III. The sedimentation rate was 17 mm. Result of the Friedman test was positive.

The diagnoses were chorea gravidarum and rheumatic endocarditis with mitral stenosis and insufficiency. It was felt that the rheumatic state was in a relatively inactive phase. No great concern was felt concerning the cardiac status as the consulting cardiologist estimated the cardiac reserve to be adequate. A high-protein diet, adequate intake of milk, calcium lactate, and vitamin supplements were advised.

A letter from the attending obstetrician elsewhere after delivery of this patient revealed the following data: She gained 12 pounds (5.4 kg.) during the entire gestation and repeated determinations of the blood pressure, urinalyses, and blood counts gave results within normal limits. When the patient was

TABLE II. SUMMARY OF FINDINGS IN

CASE	AGE	MARITAL STATUS	OBSTETRIC STATUS		HISTORY OF CHOREA		HISTORY OF RHEUMATIC FEVER OR SCARLET FEVER	HEART DISEASE	EVIDENCE OF TOXEMIA
			GRAVIDA	PARA	ASSOCIATED WITH PREGNANCY	UNASSOCIATED WITH PREGNANCY			
1	19	Married	i	0	0	1	Scarlet fever	Present	None
2	25	Married	iii	ii	2	1	Scarlet fever, rheumatic fever	Probably present	B.P. 140/85. Albuminuria, grade 2 and pyuria
3	23	Married	iv	iii	0	0	Scarlet fever	Not present	None
4	21	Married	ii	i	0	0	Rheumatic fever	Not present	None
5	19	Unmarried	i	0	0	1	None	Present	None

*Routine supportive measures were suggested to these patients.

four and a half months pregnant, chorea became more marked. Thickness of speech and marked insomnia were noted at this time. Sedation with barbiturates and bromides was provided. The most significant improvement in the chorea was noted during the last six weeks of pregnancy. The patient married during the antenatal period; the date was not stated. On July 8, 1946, after a normal labor, a 6 pound (2.7 kg.) infant was delivered by low forceps. Cyclopropane and oxygen anesthesia was used. There was no evidence of chorea in the puerperium. The follow-up examination on Aug. 22, 1946, revealed no evidence of chorea and the patient felt well.

Comment

It is impossible to draw any significant conclusions from this small series of cases. A summary of the findings is given in Table II. The average age of our patients was 21.4 years. Four were married and one was unmarried. Two were primigravidas and three were multigravidas. In all of these cases chorea began in the first half of pregnancy and lasted for periods varying from two and a half weeks to five months. All of the pregnancies were terminated spontaneously at term and six normal babies were born (one twin pregnancy).

Only one patient (in Case 1), whose condition might be described as moderately severe, required hospitalization while under our care. One other patient had been hospitalized elsewhere in the pregnancy under consideration. The therapy offered to our hospitalized patient was by no means specific and was directed essentially toward the relief of the independent or possibly associated

FIVE CASES OF CHOREA GRAVIDARUM

PSYCHOGENIC "COLOR"	CHOREA				TERMINATION OF PREGNANCY	RESULT	SUBSEQUENT PREGNANCIES
	MONTH OF PREGNANCY AT ONSET	MONTH OF CESSATION	DURATION	TREATMENT			
Not present	Approx. fourth	Approx. fifth	Approx. 2½ weeks	Sedatives, vitamin therapy, salicylates	Spontaneous	Infant living	None
Present	First half of pregnancy	Approx. fifth	Approx. 6 weeks	None*	Spontaneous	Infant living	Not known
Present	Third	Eighth (?)	At least 4 months	None*	Spontaneous	Infants living (twin preg.)	One normal pregnancy without chorea
Present	First	Sixth (?)	At least 4 months	None*	Spontaneous	Infant living	One normal pregnancy without chorea
Present	Second	Seventh	Approx. 5 months	None*	Spontaneous (low forceps)	Infant living	None

nausea and vomiting. Both complications were relieved at about the same time. Two recent publications in the South American literature referred to the use of pyridoxine (vitamin B_6) as a therapeutic agent in cases of chorea gravidarum with gratifying results. We used this agent in the treatment of the hyperemesis in this case but also used other measures, so any evaluation of the therapeutic effect of pyridoxine in this condition is impossible.

No evidence to support a toxemic etiology of this condition was present in this series, other than perhaps the nausea and vomiting mentioned in two cases. A rheumatic background was present in all of the cases. A past history of chorea was given in three cases and of rheumatic fever in two cases. Heart disease was present in three cases. In Case 3, a patient who did not give a history of chorea or rheumatic fever and had no evidence of heart disease had had scarlet fever and several episodes of tonsillitis as a child which might be classified as a rheumatic-equivalent type of background. In the terminology of Weigner,[7] psychogenic "color" was noted in four of the five pregnancies.

Summary

The recent literature concerning chorea gravidarum is considered. Reference is made to the toxemic, allergic, rheumatic, infectious, and psychogenic hypotheses of origin of chorea gravidarum. The current status of authoritative obstetric opinion is reviewed. Five cases of chorea gravidarum observed at the clinic are presented. The case for a rheumatic etiology of this condition is further strengthened by these reports. A suggestion of psychogenic "color" was present in this series. Conservative methods of treatment and delivery were used in all cases. A successful outcome of the pregnancy occurred in all instances.

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NEWER OBSTETRIC ANALGESICS*

Preliminary Evaluation of Compounds No. 10720 and No. 10820 (Dolophine)

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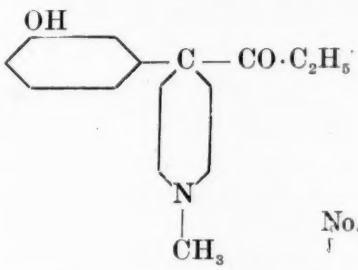
DEMEROL was the first of what appears to be a long line of potent new analgesic agents. Some of these were prepared by German chemists and were acquired by this country during the war. Recently, the U. S. Department of Commerce released information concerning these drugs in report No. 981,[1] which describes compounds No. 10720 and No. 10820, as well as many others which may have clinical value. The purpose of this report is to suggest methods of evaluation of obstetric analgesics and to present results of investigations upon the two mentioned compounds.

Between 1930 and 1940, many new barbiturates were compounded, and nearly every one was highly recommended by someone, as the perfect obstetric analgesic. Yet, today, the champions of those drugs have discarded them in favor of the newer synthetic analgesics, e.g., Demerol. These past experiences must prevent unwarranted enthusiasm by all who share in the development of new analgesics. Nevertheless, it is important that promising new compounds be carefully investigated.

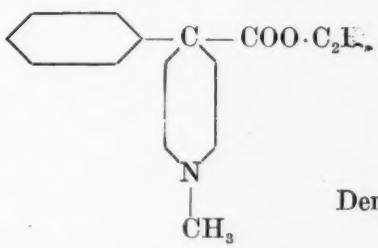
To evaluate any analgesic properly, it is well to consider the qualifications of a perfect obstetric analgesic. Such a drug would give complete analgesia, with complete safety to mother and baby, without interference with the normal processes of labor and delivery. Furthermore, it should be inexpensive, easily administered, and readily used in any environment. Such an agent does not exist, and perhaps never will; yet these are criteria by which all new obstetric analgesic agents should be tried.

Pharmacology

Compound No. 10720 is strikingly similar to Demerol. Instead of having a carboxyl group as does Demerol, it is a ketone. In addition it has an OH added to the benzene ring.



No. 10720



Demerol

*Presented, by invitation, at a meeting of the New Orleans Obstetrical and Gynecological Society, Nov. 6, 1947.

Very little is known concerning the pharmacology of this drug. Only brief reports have appeared in the literature.[2, 3] These studies indicated that this compound and several similar synthetic analgesics depressed blood pressure, salivation, and the heart rate of experimental animals. The effect on respiration varied—No. 10720 did depress respiration in the rat. The suggested dosage in man was about 7.5 mg.

Dolophine (No. 10820) is only slightly different in structure. It is a diphenyl butanone compound which is being rather widely investigated at present. The suggested dosage of this drug has been from 5 to 10 mg.

Results

The results are based on observations of 50 obstetric patients who received compound No. 10720* and of 18 who received Dolophine (No. 10820)* during labor. Dolophine was used first, but was discarded as inferior when No. 10720 became available.

Material

No attempt was made to select the patients for this study, although it is obvious that some selection is inevitable. For example, analgesics of any kind would not be given to a woman in premature labor, unless complications of pregnancy or labor so demanded. The data will show that even closer adherence to such principles might have produced better results.

Slightly more than half of the patients were "house cases," and the remainder were private patients. There were 30 primiparas and 20 multiparas, most of whom (88 per cent), according to menstrual history, were at term. The remainder were from two to four weeks from term. A third of these mothers had complications of pregnancy, such as toxemia, heart disease, diabetes, iso-immunization, jaundice, previous cesarean section, and the like.

Dosage

Five to ten mg. of compound No. 10720 (hereafter to be called No. 10720) had been tentatively suggested as a possible therapeutic range. The smaller one was chosen, and it proved to be satisfactory. Later, the dose was increased to 7.5 and finally to 10 mg. Although the larger doses were well tolerated by the mother, there were some undesirable fetal effects, which will be discussed later. Administration was by hypodermic.

In nine of the patients, the drug was repeated. As a rule, the succeeding doses were spaced at least four hours apart. (More recently, a patient not included in this report received four successive doses within a twenty-four hour period, with good effect, and without apparent harm to mother or baby.)

Finally, the drug was combined with 1/200 or 1/300 grain of scopolamine. The importance of this combination will be discussed subsequently.

Onset and Duration of Action

By action, we mean the onset of appreciable obstetric analgesia, and it does not refer to maximum analgesia. Only an occasional patient noted subjective relief within fifteen minutes. With very few exceptions, this effect was present within thirty to forty-five minutes after the administration (Table I). This table also shows that the duration of action was as sharply limited as was

*Supplied through the courtesy of Eli Lilly & Co., Indianapolis, Ind.

its onset. Only nineteen patients could be fully observed. The others were delivered while the drug was still effective; so duration could not be determined. No patient had analgesia for more than three and one-half hours, but most patients obtained from two and one-half to three hours of relief.

TABLE I. ONSET AND DURATION OF ANALGESIA

ONSET		DURATION		
15 minutes	2	1½ hours		0
30 minutes	14	2½ hours		6
45 minutes	16	3½ hours		13
60 minutes	4	No data		12
No data	14	Delivery intervened		19
	—	1½ hours	3	
	50	2½ hours	14	
		3 hours	2	
			—	
			19	
				—
				50

Untoward Effects

These were infrequent. Many mothers noted some dryness of the mouth and some were giddy. Neither of these effects was annoying. Three had nausea and emesis. Perhaps this was from the drug; yet such gastrointestinal disturbances are not uncommon in labor, without medication. One complained of vertigo, as distinguished from the lightheaded, giddy sensation which was common. There were no other subjective complaints.

Such objective measurements as pulse, respiration, blood pressure, and fetal heart rate were recorded before and during treatment. Early in the study, these vital signs were repeatedly observed, but as the study progressed without the appearance of significant changes, we became less exacting. Approximately half (23) of the patients had detailed observation. One patient had a decrease in pulse rate from 70 to 62; another had a slight slowing of respirations; and one other had a drop in blood pressure from 130/80 to 120/70. There were no clearly demonstrable changes in the fetal heart rate due to the drug.

In no patient did we observe excitation produced by the drug. Two of the mothers were wildly excited before No. 10720 was given and this persisted in spite of therapy. On the other hand many mothers had marked relief from their apprehension and were able to sleep and rest between contractions even though analgesia was incomplete.

Analgesic Effects

Under this heading we will consider the three qualities of an obstetric analgesic agent: (1) analgesia, (2) amnesia, and (3) rest.

Analgesia could be studied in 46 patients—the others delivered before effect could take place, i.e., within thirty minutes. Table II lists the results. Of the entire group, about half had satisfactory analgesia (20 per cent excellent and 30 per cent good); the other half had fair analgesia or none at all (40 per cent fair and 10 per cent none).

Of considerable interest was the improvement in analgesia which followed the combination of scopolamine with 5 mg. of No. 10720. In this small group of 13 mothers, 85 per cent had satisfactory analgesia; 15 per cent had partial success, and there were no failures. In one patient, 5 mg. of No. 10720 was combined with 1/200 grain scopolamine. This produced good analgesia. About five hours later, 7.5 mg. of No. 10720 alone was given and this produced

only fair analgesia. In another five hours the first combination was repeated and again good analgesia was produced. Whether this is a synergistic action or not could not be determined from this study. Scott et al.[3] did not observe improved analgesia with the addition of scopolamine.

Rest and sleep between uterine contractions frequently followed the use of No. 10720. Nearly 30 per cent had excellent results which meant that the patient slept between contractions. A slightly greater number (37 per cent) had good results (Table II).

The combination of 1/200 grain of scopolamine with 5 mg. of the drug apparently improved the effect.

Amnesia is not a property of drugs of this type; so we did not make special tests in an effort to determine this effect. Nevertheless, patients occasionally noted that they could not remember when they went to the delivery room, or the time of day, etc. Scopolamine does produce amnesia; so the mothers who received it were considered separately. When scopolamine was given, approximately half had fair amnesia, but without it there was no significant amnesia.

TABLE II. ANALGESIA AND REST IN RELATION TO DOSAGE

ANALGESIA	5 MG.	5 MG. PLUS SCOP. 1/200	7½ MG.	10 MG.	TOTAL
None	1	0	0	0	1
Poor	2	0	1	0	3
Fair	12	2	2	2	18
Good	7	6	1	0	14
Excellent	1	5	3	1	10
Not evaluated	2	1	0	1	4
	25	14	7	4	50
REST					
None	0	0	0	0	0
Poor	3	0	1	0	4
Fair	8	3	0	1	12
Good	7	6	2	2	17
Excellent	5	4	4	0	13
Not evaluated	2	1	0	1	4
	25	14	7	4	50

Effect on Labor

There is probably no more difficult observation to make than to determine the effect of any given drug on the duration of labor. So many variables are present that significance of any one is easily lost. To measure the effect of a drug in terms of duration of labor means a consideration of the effectiveness of uterine contractions, the state of the cervix and other soft tissues, the configuration of the bony pelvis and the size of the baby. Even if all of these could be measured, we still have no satisfactory method of determining the onset of labor.

Most labors gather momentum as they progress, but the amount of this increase and the time of its appearance cannot be predicted. There are, of course, many exceptions, such as secondary uterine inertia. In this study, we have attempted to evaluate the effect of No. 10720 on uterine contractions in the negative sense. That is, to ask: Was there a diminution in the frequency, intensity, and duration of contractions following the use of the drug?

With the foregoing qualifications in mind, our observations indicate that six mothers had a mild temporary diminution in the frequency of contractions. Three showed some temporary reduction of intensity of contractions. None

showed significant change in the duration of contractions. Of 39 women who received the drug during active labor, after cervical dilatation was under way, 34 were delivered in less than four hours and about half were delivered in less than two and one-half hours.

Delivery

Many methods of obstetric analgesia interfere with the normal mechanism of delivery, so that operative intervention frequently becomes necessary. No such tendency was evident in this study. Of 30 primiparous patients, 21 delivered spontaneously. There were 9 forceps deliveries; 5 were done electively because of complications of pregnancy; 2, and possibly a third, were done because of lack of progress in the second stage of labor, in spite of good contractions and excellent cooperation, and only one because of poor cooperation associated with effects of analgesia. Of the 20 multiparous patients, 2 low forceps deliveries were done. In both, the indication happened to be the same, previous cesarean section.

Blood Loss

Most of the women lost less than 300 c.c. of blood (estimated). Two had postpartum hemorrhage, but in neither case was the drug at fault.

Anesthesia

Frequently analgesics are blamed for effects produced by anesthesia at delivery. The converse is equally true. For this reason, no general anesthesia was produced. About two-thirds of these patients received nitrous oxide-oxygen analgesia combined with local anesthesia, and the remainder had local anesthesia or none at all.

Neonatal Asphyxia and Mortality

There is no standard classification for neonatal asphyxia. Something more than the textbook descriptions of asphyxia livida and asphyxia pallida is necessary. For a period of years we have used the following classification (Table III) which, although strict, is not too difficult to apply clinically. It is especially important that strict standards be used in the evaluation of analgesic agents.

TABLE III. CLASSIFICATION OF ASPHYXIA NEONATORUM AS USED IN THIS STUDY

PHYSICAL SIGNS		NO ASPHYXIA	MILD ASPHYXIA	MODERATE ASPHYXIA	SEVERE ASPHYXIA
Respiratory	Onset respiration	Spontaneous, immediate	Spontaneous oligopnea 1 to 5 min.	Delayed apnea 5 to 15 min.	Delayed apnea over 15 min.
	Resuscitation	None	None	Tracheal tube or mouth-to-mouth	Tracheal tube or mouth-to-mouth
Activity	Cry	Vigorous, lusty	Delayed, vigorous, lusty	Delayed, weak	Weak or absent
Cyanosis		None	Mild	Moderate	Severe or pallor
Muscular activity		Vigorous, active	Sluggish	Depressed	Flaccid and relaxed
Pallor and/or shock		None	None	None	Present

Fifty mothers were delivered of fifty-one babies. There were no stillbirths and three neonatal deaths. Two of the deaths were due to congenital disease incompatible with life, and the third infant died of meningitis. It is obvious that the drug was not a significant factor in these deaths.

The incidence of neonatal asphyxia was low. Eighty-two per cent of the babies were normal; 12 per cent had mild asphyxia; 6 per cent had moderate asphyxia, and there was no severe asphyxia.

Two easily measured objective signs were used in this classification of asphyxia: the onset of respirations, and the appearance of the characteristic lusty cry. Any infant who breathed spontaneously, in less than fifteen seconds "by the clock," was classified as having immediate respiration. This is about the usual length of time required to complete the delivery and to upend the baby for drainage of mucus and amniotic fluid. Forty-one had immediate respiration (Table IV). Two were delayed five minutes and four were delayed between two and three minutes.

TABLE IV. ONSET OF RESPIRATIONS AND CRYING

	RESPIRATIONS	ACTIVE CRY
Immediate	41	33
Within ½ min	1	–
Within 1 min.	1	3
Within 2 min.	3	3
Within 3 min.	1	2
Within 4 min.	0	0
Within 5 min.	2	3
Within 10 min.	0	2
Within 15 min.	0	2
No data	2	3
Total babies	51	51

The significance of the *active* cry for classification of asphyxia has not often been used and might be questioned by some as invalid. It is certain that perfectly normal babies without asphyxia and with normal respirations and color may fail to cry immediately or occasionally for several minutes. On the other hand, we have observed for many years that a delayed cry frequently indicates depression below the level of asphyxia. Before the baby can actually cry it must breathe; so we have classified as immediate any cry within thirty seconds after delivery. Two-thirds of all babies had an immediate cry, and the remainder were distributed rather evenly through the first fifteen minutes of life. One failed to cry—an infant with congenital absence of the diaphragm.

Many factors other than analgesia can produce neonatal asphyxia. Consequently each asphyxiated infant was carefully evaluated for cause of asphyxia.

Of the nine babies under consideration, two had congenital lesions responsible for asphyxia. Three were asphyxiated by difficult delivery. The drug was at fault in four cases, about 8 per cent. It produced three mildly asphyxiated babies and moderate asphyxia in one.

The next step was to determine in what way the drug was to blame. Was it a question of timing in relation to delivery? Was it dosage? Was it faulty evaluation of the patient as an asphyxial risk?

It is a well-established fact that small infants tolerate analgesics poorly. When these infants are sorted according to weight (Table V), it is evident that three of the four babies with asphyxia due to the drug were from a group of nine weighing less than 2750 Gm.

There was good evidence that dosage was also a factor in asphyxia. Forty mothers receiving no more than 5 mg. of No. 10720 as a terminal dose produced one mildly asphyxiated baby, while three were produced by eleven mothers who had received 7.5 or 10 mg. of No. 10720.

TABLE V. ASPHYXIA AND WEIGHT OF INFANT

WEIGHT IN GRAMS	TOTAL	ASPHYXIA
2250 to 2500	4	1 (d)
2500 to 2750	5	2 (2d)
2750 to 3000	6	1
3000 to 3250	11	4 (1d)
3250 to 3500	10	1
3500 to 4000	14	0
No data	1	0
	51	9 (4d)

(d) Asphyxia due to drug.

The relationship of "drug asphyxia" to the difference between time of administration and delivery is not clear. All of the babies so asphyxiated were delivered from one to three hours after the mother received the drug, but the majority of the babies were also delivered during this same time. If a time relationship exists, more experience will be necessary to establish it.

Special mention might be made of one group of twenty-one private patients who were included in this study. All but one received 5 mg. of the drug, usually combined with scopolamine. A general attempt was made to see that the drug was not administered to women with small babies and to those who would deliver within two hours. Every baby but one in this group breathed immediately, and one breathed in thirty seconds. Fifteen cried immediately, three in one minute, two in two minutes, and one in five minutes. The latter was mildly asphyxiated.

Results With Dolophine (No. 10820)

Dolophine was administered to 17 obstetric patients. The amount given ranged from 5 mg. to 15 mg. with a usual dose of 7.5 mg. Analgesia, such as it was, appeared in approximately one-half hour. The effect, when present, persisted for about two hours.

Untoward side reactions were not noted. Two women had nausea, and one was wildly excited. The excitation was present before, as well as after, use of the drug.

Twelve of the seventeen were observed closely for changes in pulse, respiration, blood pressure, and fetal heart rate. None were noted.

Analgesic effects were disappointing. There was no excellent nor good analgesia; one only had fair analgesia, while 7 had poor results, and 9 were failures. There was no amnesia. Rest was obtained in 11 patients; 6 had fair results, and 5 had poor rest.

There was no visible effect of the drug on the frequency, duration, or intensity of the contractions.

Two infants were mildly asphyxiated. The cause in one was trauma and, in the other, the drug (15 mg.) was to blame.

Discussion and Summary

These preliminary investigations have convinced us that compound No. 10720 is worthy of further trial as an obstetric analgesic. Dolophine (No. 10802), in our hands, has not been a useful agent.

From the results described, we have formulated a general plan for the use of this analgesic. It is well to wait until the patient is in active labor and in genuine discomfort before the drug is given. On the other hand, too much de-

lay permits labor to advance to a point where the drug cannot overcome the pain of the strong uterine contractions. Some of the poor results came when this error was made. The most satisfactory dose of No. 10720 is from 5 to 7.5 mg. This corresponds roughly to 100 mg. of demerol. Larger doses, 7.5 to 10 mg., may be given to mothers with normal-sized infants, if delivery is not imminent within three hours. The combination of 5 mg. of No. 10720 with 1/200 grain of scopolamine produced results comparable to those which followed the use of 7.5 mg. alone. The peak of analgesia is apparently reached in one and one-half hours, and most of the effect is lost within three hours. Thus the drug should not be given oftener than every three hours.

Generally speaking, it may be said that analgesia is satisfactory. Although we did not make direct comparisons with Demerol, which has been used for many years on this service, many of the staff think the new drug to be equal or superior.*

After administration of No. 10720, the patients usually become sleepy, and often they sleep soundly between contractions. With the onset of a contraction, they usually rouse and are aware of some discomfort. Excitement was not noted, and nearly every patient was able to cooperate fully, a fact of particular significance during the second stage of labor.

There was no evidence of interference with the effectiveness of the uterine contractions. About three-fourths of the women observed completed their labor in less than four hours after medication. This fact, combined with the fact that we attempted to give the drug before labor was far advanced, suggests that labor was not prolonged. The obstetric literature is replete with reports that this or that analgesic shortened labor. Before such statements can be considered valid, careful controls must be had from the same type of obstetric material in the same clinic. This we did not do.

Did the infants have to pay a price for the pain relief of their mothers? They probably did, but there was little evidence to indicate that they paid too much. There were three neonatal deaths, none of which could be attributed to the drug in any way.

There were nine asphyxiated infants (18 per cent). There were no controls with untreated mothers; however, we have previously expressed the incidence of asphyxia neonatorum in such patients,[3, 4] at about 10 per cent, with a distribution 5 per cent mild, 4 per cent moderate, and 1 per cent severe asphyxia. In the present report there was 18 per cent asphyxia, with a distribution of 12 per cent mild, 6 per cent moderate, and no severe asphyxia. This suggests that No. 10720 causes some increase in mild asphyxia, which is of no great clinical significance. The fact that moderate and severe asphyxia are apparently not increased is of great clinical significance.

It was possible to assign four of the nine cases of asphyxia to the drug. Three of these were mild and one was moderate. The appearance of asphyxia in babies weighing less than 2750 grams again confirms the fact that small in-

*One patient in this group received No. 10720 as well as Demerol during labor. One hundred mg. of Demerol given during early active labor produced fair (2 plus) pain relief. Later in labor, 5 mg. of No. 10720 produced good (3 plus) pain relief.

fants tolerate analgesics poorly. Furthermore, 2 of these 3 mothers received 7.5 and 10 mg. of the drug, respectively. In retrospect, it is evident that the larger doses of No. 10720 should not have been given to mothers with small infants.

Judgment follows experience, and skill is the result of technique and practice. Both are necessary for the proper use of all methods of obstetric analgesia. Therefore we believe that the clinician who is not prepared to undertake a controlled investigative procedure should not forsake familiar standard practices until the value of a new drug is proved.

Conclusions

1. A new phenyl-piperidine compound similar to Demerol, as yet unnamed, but called compound No. 10720, has been tried as an obstetric analgesic in fifty labors.

2. The drug had few side reactions, and toxic manifestations were not seen.

3. Analgesia was fair to good in about two-thirds of the patients treated with 5 mg. of No. 10720. The addition of 1/200 grain of scopolamine seemed to enhance the analgesia. Amnesia was rarely present unless scopolamine had been given.

4. Asphyxia neonatorum was not a problem. Although there was some increase in mild asphyxia, there was no severe asphyxia, and only the usual amount (about 5 per cent) of moderate asphyxia.

5. Dolophine (No. 10820) was used in seventeen patients. As a whole, the results were disappointing.

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A METHOD OF OBSTETRIC ANALGESIA AND ANESTHESIA*†

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ALTHOUGH no one ideal method of obstetric analgesia and anesthesia has been presented, it is thought that the combination to be described (Demerol and scopolamine) fulfills many requirements. The object of this study was the attainment of a simple, adequate method of obstetric analgesia which is safe enough to have wide application and adequate enough to provide analgesia and anesthesia for normal labor and outlet or low forceps delivery.

For the procedure selected, two drugs were employed which have a general analgesic and amnesic effect on the patient in the earlier stages of labor. Demerol was used for analgesia and scopolamine for amnesia. Since these alone are usually inadequate for the perineal stage and repair, local anesthesia in the form of a pudendal nerve block was selected. Demerol has been used in combination with scopolamine for the first and second stages of labor.[1, 2] For the delivery and repair, a 1 per cent Intracaine solution was used for nerve block. General anesthesia has a depressing effect on the infant, and it is undesirable to administer a general anesthetic agent to the unprepared patient. Demerol, therefore, was chosen because it lacked respiratory depression in the therapeutic dosage when used with a pudendal block. Intracaine was chosen for pudendal block because it displays a more rapid action than procaine hydrochloride, yet it produces anesthesia of greater duration.[3] Although the principle of pudendal block is not new,[4] a simplified method is presented to permit its universal acceptance. Today, one-half of American women are delivered in the home, and nursing staffs of most hospitals are still feeling the effect of war shortages. This combination requires a minimum of professional and nursing care, yet allows the patient safe conduct through her first stages of labor with analgesia and amnesia, which is obtained by using Demerol and scopolamine. Minor obstetric procedures such as spontaneous delivery with episiotomy or low forceps may easily and safely be carried out by the use of pudendal block with Intracaine.

Technique

The foundation for a safe, painless delivery is an adequate psychological approach to childbirth as a physiologic phenomenon. If the developed fears of

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the expectant mother can be minimized, one may enjoy complete cooperation throughout labor. When the uterine contractions elicit severe pains during the first stage of labor, a rectal examination is performed to determine the condition of the cervix and the progress of labor. If the cervix is dilated 4 cm. or more and strong painful contractions are present, Demerol and scopolamine are given. Demerol, 1 mg. per pound of body weight, and scopolamine hydrobromide, $\frac{1}{150}$ grain, are now administered intramuscularly. Although mixing these solutions is not recommended, Demerol can be given intravenously, if desired, without harmful effects. Most patients will obtain moderate to complete relief of pain for from two to four hours without any significant retardation in labor. After this period, additional analgesia may be required and safely repeated, provided the progress of labor is satisfactory. Occasionally, sensitivity to scopolamine may make it desirable to reduce the amount of scopolamine to $\frac{1}{200}$ grain to prevent irrational behavior.

When the progress of labor has advanced and rectal examination reveals that the cervix is completely dilated in the multiparous patient, or the perineal stage is reached in the primiparous patient, preparation for delivery and pudendal block is completed by placing the patient on the delivery table in the lithotomy position. Since the effectiveness of this technique lies in adequately blocking the pudendal, ilio-inguinal and inferior hemorrhoidal nerves, knowledge of their anatomic distribution is essential. The pudic nerve (n. pudendus) is the principal nerve supply of the perineum. Its origin in the pelvis is usually from three roots arising from the second, third, and fourth sacral nerves. The pudendal nerve passes to the buttock through the great sacrosciatic foramen below the great sciatic nerve and lies on the lesser sacrosciatic ligament or the spine of the ischium. It is mesial to the internal pudic artery and enters the perineum with the pudic artery through the small sacrosciatic foramen. In the perineum, it is deeply placed in the outer wall of the ischiorectal fossa, enclosed in a special sheath derived from the parietal pelvic fascia called Alcock's canal, which contains the pudic nerve, artery, and vein. It is at this point, mesially to the ischial tuberosity, where the pudendal nerve is blocked, and not at the usual site at the spine of the ischium. Occasionally the inferior hemorrhoidal nerve has an independent origin from the plexus and merely accompanies the pudic nerve in the first part of its course. The cutaneous branch of the ilio-inguinal nerve which innervates the skin over the symphysis, the mons veneris, and labium majus forms continuous branches with the pudendal or pudic nerves. For this reason, the ilio-inguinal and inferior hemorrhoidal nerves are given special attention.

Surgical preparation of the perineum includes cleansing the previously shaved area with soap solution. Zephiran solution, 1:1,000, is used for the skin antiseptic, after which sterile drapes are applied. The sterile pudendal-block kit is then opened and the solution prepared by placing 1 Gm. of Intracaine crystals in a flask containing 100 c.c. of distilled water. To this, five drops of epinephrine solution, 1:1,000, is added. The rectum is covered and a skin wheal is raised on each side of the perineal body with a hypodermic needle, using Intracaine. This blocks the cutaneous nerves to the perineum from the inferior pudic nerve. The left index finger is inserted into the vagina and pressure is exerted to the left and laterally to the tuberosity of the ischium, thereby, compressing Alcock's canal. Through the skin wheal. the 3 inch, 20 gauge, needle is directed to Alcock's canal. It is guided into this position by the left index finger and the tuberosity of the ischium. When this site is located and after the preliminary aspiration, 10 c.c. of 1 per cent Intracaine solution is injected along the pudendal nerve. Without removing the needle, the 10 c.c. syringe is disconnected and refilled, reconnected to the needle which is withdrawn almost to

the tip and redirected to the symphysis. After aspiration, the ilio-inguinal nerve is blocked with 10 c.c. of Intracaine solution as the nerve passes over the symphysis. Again the syringe is disconnected and refilled with solution, replaced on the needle and directed toward, *but not into*, the sphincter ani muscle. Here 10 c.c. of solution are deposited in the levator fascia following aspiration, so that the inferior hemorrhoidal and branches of the fourth sacral nerves are blocked. This procedure is repeated on the other (right) side. After about five minutes, perineal relaxation is obtained and anesthesia is thus established. Skin test for satisfactory anesthesia is performed and its extent noted. A gauze sponge is clamped to the perineum so that the rectum is covered to prevent any contamination. This step further confirms satisfactory perineal anesthesia. Episiotomy may then be performed while rational conversation is exchanged with the patient. Labor may progress normally, or low forceps may be indicated with the completion of the second stage, and the third stage can be completed. Since the pudendal block does not eliminate sensory impulses from the cervix, undue traction must be avoided during its inspection. Should this procedure prove painful, or extensive cervical repair be necessary, 100 mg. of Demerol, given intravenously, will allow extensive surgical repair of the cervix, vagina, perineum, or rectum.

The series consisted of 100 study patients and 100 control patients divided into 60 primiparas, 40 controls, and 40 multiparas and 60 controls. Only patients who had normal spontaneous delivery were selected for controls after delivery and not at random on admission. The cases for study were selected at random on admission; the criteria were a normal pelvis and a prospective normal delivery.

Complications in the study group existing at the onset of labor were: mild pre-eclamptic, 10, cardiac, 1, multiple pregnancy, 1, premature labor, 2, and tracheobronchitis, 1. In the control group there was 1 premature labor. Complications and surgical procedures during labor in the study group were: twins, 1, persistent occiput posterior, 1, elective outlet forceps, 17, surgical forceps, 2, spontaneous breech, 1, and secondary uterine inertia, 1. The controls showed no complications of labor since they were selected after delivery. There were no serious complications of labor and there was no maternal mortality. The maternal morbidity in the study group included postpartum hemorrhage, 2 cases, mild endometritis and parametritis, 7 cases, infected episiotomy, 1 case, retained secundines, 2 cases, and ischiorectal abscess, 2 cases. The control group included 10 patients with parametritis and 2 with ischiorectal abscess.

Fetal Mortality

Two fetal deaths occurred in the test group, a fetal mortality of 2 per cent. Both of these were neonatal deaths resulting from intracranial trauma. In Case 1, precipitate delivery, neonatal death occurred thirty-six hours after delivery. The infant had received continuous oxygen therapy after thorough aspiration. Postmortem examination disclosed bilateral tentorial tears and atelectasis in four lobes of the lungs. Consequently, the method of anesthesia was not responsible for the death.

Case 2 was also a neonatal death, which occurred eleven hours after delivery of a premature infant whose birth weight was 2 pounds 15 ounces. This infant was cyanotic and received oxygen and incubator care. Postmortem examination revealed a subdural hemorrhage; consequently, the method of analgesia was not responsible for this death.

The duration of labor in the 60 primiparas of the test group ranged from three and one-half hours to twenty-four hours; in the control group it varied from six and one-half hours to twenty-four hours (Fig. 1). In the test group of 40 multiparas the duration of labor ranged from one and three-fourths hours to twenty-eight and one-half hours, while in the control group it ranged from one and three-fourth to fifteen hours (Fig. 2). The average dosage used was 1 mg. per pound of body weight. This was repeated in two hours when necessary, since the effective duration was from two to four hours. Consequently, the total average dose was 200 milligrams.

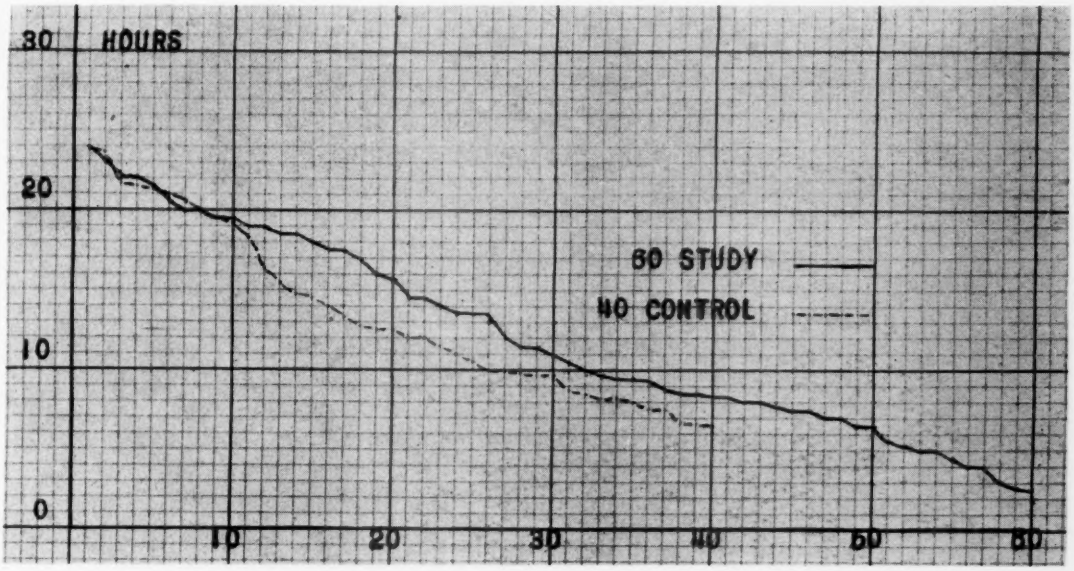

Fig. 1.—Duration of labor—primiparas.

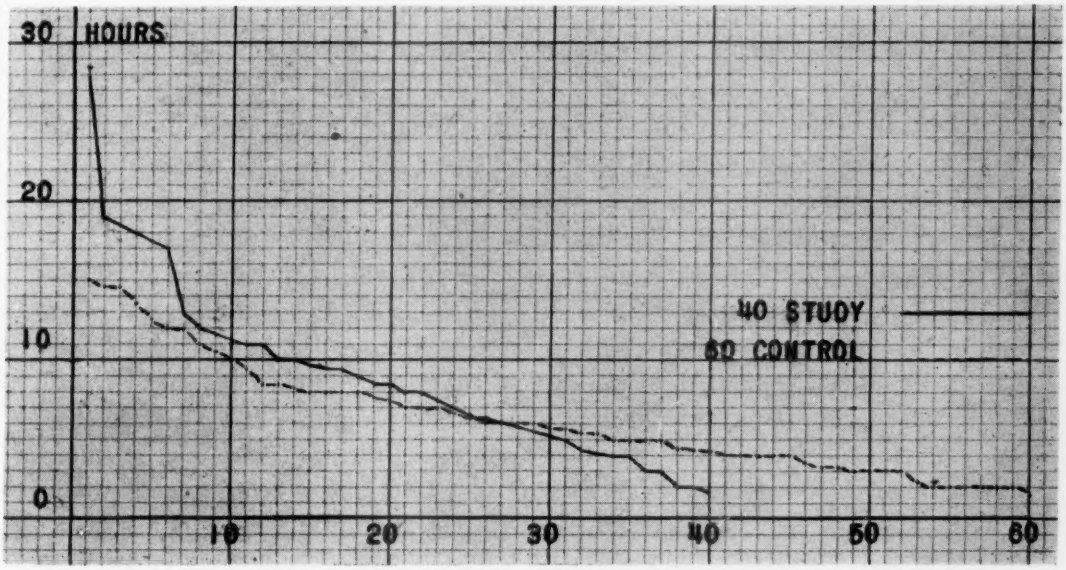

Fig. 2.—Duration of labor—multiparas.

The Result of Analgesia and Anesthesia

Satisfactory anesthesia was demonstrated by skin test and by a statement of the patient twenty-four hours later to the same impartial observer (Table I).

TABLE I. EFFECTIVE ANALGESIA

	SATISFACTORY	UNSATISFACTORY
Study group	90	10
Control group	50*	50

*Some had nitrous oxide and oxygen at birth of head.

Comment

The use of Demerol for analgesia is a contribution to obstetric practice. In the dosage recommended, it may be considered safe when given within one hour of delivery if local block is used for the second stage of labor. The following contraindications exist:

1. Local infection of the perineum, bacterial or fungus (at the site of injection). Included are cryptitis and infected thrombotic hemorrhoids.
2. Hysteria, epilepsy, or emotional instability.
3. Obstetric complications (about 4 per cent of hospital patients).
   a. Placenta previa.
   b. Placenta abruptio.
   c. Cephalopelvic disproportion, unless the Demerol and scopolamine are used as analgesics during a test labor.
   d. Birth of monstrosities.
   e. Patients with unengaged head or false labor.
   f. History of previous sensitivity to either drug—exceedingly rare.

No attempt was made to study the effect of Demerol on pre-eclamptic patients. Ten such patients with mild to moderate symptoms showed no unusual reactions.

The intravenous method of administering Demerol is not contraindicated in the recommended dosage. Regardless of the speed of intravenous administration, no deleterious reactions were observed in over 200 injections. There was no infant or maternal mortality, nor was there infant respiratory depression. Slight depression of the infant has been known to occur when barbiturates or nitrous oxide and oxygen were used. Intracaine is ideal, since it is a quick-acting local anesthetic of long duration. With proper technique, the area of anesthesia extends two-thirds the length of the vaginal canal, and visible relaxation through the perineum may be noted. No fear of respiratory depression need exist, since the patient is able to converse with her obstetrician during the repair. Demerol may be used in obstetrics without fear of addiction, and it requires a minimum of obstetric experience to determine accurately the optimal time for Demerol analgesia and the performance of a pudendal block. The technique has been simplified so that the pudendal nerve is blocked at its *exit* from Alcock's Canal.

This series has shown that three conditions must be present: (1) reasonable emotional stability in a patient who has not become irrational from too much scopolamine; (2) an adequate knowledge of the anatomy of the perineum by the physician, and (3) vigilance to aseptic technique and consciousness that this is a local anesthesia. When these qualifications are fulfilled, a wide variety of common obstetric procedures, including episiotomy, low forceps, and perineorrhaphy, may be performed.

Summary

A safe, simple, efficient method of obstetric analgesia and anesthesia has been described, using some new synthetic drugs. The large factor of safety of Demerol in combination with scopolamine and Intracaine offers a procedure without any of the hazards of the more common types of anesthesia, particularly when the services of a professional anesthetist are not available. The simplicity of this technique is apparent when an elementary knowledge of the anatomy of the perineum is acquired. It is effective when the nerves are blocked and allows most minor procedures, including outlet forceps delivery and repair.

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Discussion

DR. NEWLIN F. PAXSON.—This was a project we have been working on at Hahnemann with the idea of trying to find a safe procedure that would have application not only in the large hospitals, but in the small hospitals, and in the homes, where elaborate preparations are not possible. It seems to be a fairly practical method.

The reason for the selection of the particular drugs used is that they fulfill most nearly the requirements of simplicity and efficiency. The barbiturates cause too much restlessness; also, when they are supplemented by nitrous oxide and oxygen administered by an unskilled anesthetist, deaths have followed.

The occurrence of two ischiorectal abscesses is due primarily to the blocking of the sacral nerves. This particular hazard can be overcome by injection around the anus subcutaneously. The needle enters the original wheal and is pointed toward the anus; 5 c.c. of Intracaine is then injected above and lateral to the anus.

There is one interesting thing I observed, the report of satisfactory analgesia on the part of controls who received little or no analgesia at all, except inhalation for the perineal stage. The only way we have of estimating the results of a method of obstetric analgesia is to ask the patient whether the method is satisfactory. Apparently a great many women are satisfied with any method that does not leave them uncomfortable for a long period. This may explain why so many methods are reported as satisfactory.

DR. DWIGHT GROVE.—My discussion tonight will be more from the standpoint of anesthesiology than from obstetrics. It is generally said that Demerol produces more analgesia with less respiratory depression than any of the more commonly used analgesic drugs. My experience would tend to bear out this statement. However, that Demerol can produce severe respiratory depression is illustrated by a case from our records. A 39-year-old multipara,

weighing 170 pounds, was given 200 mg. of Demerol. This patient was in good physical condition. Physical examination was essentially negative with pregnancy at term. At the end of approximately fifty-five minutes of active labor, she was given 200 mg. of Demerol intravenously, the time during which it was administered being approximately one and one-half minutes. During the period of injection, conversation was carried on between the operator and the patient. Immediately following the administration of the Demerol, scopolamine hydrobromide, with 1/200 grain in the syringe was started intravenously. To give this injection was to take two minutes. By the time one-half of the scopolamine was injected, the patient had ceased talking, showed mild cyanosis, and absence of any respiratory efforts. Oxygen was administered and at first it was necessary to inflate the lungs a few times. Then she began to breathe spontaneously at the rate of four per minute. Her respiratory rate gradually increased so that by the end of two hours the rate was 8 per minute. Twenty minutes after the Demerol was given, the patient delivered spontaneously without any additional anesthesia. The baby cried vigorously at birth.

There have been occasions, however, when we have been suspicious of some degree of respiratory depression from Demerol in the newborn. On the matter of the nerve supply to the perineum, there is one additional nerve that should be described, the inferior pudendal nerve. This arises from the posterior femoral cutaneous or small sciatic nerve near the lower border of the gluteus maximus muscle and passes downward and in front of the tuberosity of the ischium and continues anteriorly in the subcutaneous tissue of the perineum to supply the scrotum in the male and the labium majus in the female. Failure to block this nerve will result in inadequate anesthesia of the perineum. Also, in the diagram showing the placement of the needles, I do not believe the fact was mentioned that the needle was directed subcutaneously toward the symphysis. It does not go beneath the deep fascia because the terminal filaments of the ilio-inguinal nerve are in the subcutaneous tissue. The use of Adrenalin was mentioned, and I mention it now to endorse it heartily. We make it a practice with few exceptions to add Adrenalin to local anesthestic agents. The matter of aspiration cannot be overemphasized. An additional procedure to make certain that a needle is not within a blood vessel is to aspirate while rotating the needle through a circle, aspirating about one time in every quadrant as the needle is rotated. It is possible for a needle to be within a blood vessel and on aspiration to have no blood appear in the syringe for the simple reason that the intima of the blood vessel is drawn against the needle, thereby blocking it. It is unlikely that a needle will be in a blood vessel after having aspirated repeatedly while rotating the needle through a complete circle. I consider the use of pudendal block a valuable procedure and particularly useful in those circumstances in which facilities are limited.

DR. ROBERT M. HUNTER.—I think I should say something concerning the six cases of ischiorectal abscess reported by Dr. Schadel.

I happened to be on service at the time, and feel that it was lack of training on the part of the interne staff that produced the abscesses. He did not, but should have defended himself. He should have stated that in the cases he personally supervised no ischiorectal abscess developed. The interne failed to realize the displacement of the rectum during the last stages of labor, and thus the needle inadverently perforated the roof of the rectum.

This error has been corrected and since that time we are glad to report there has been no further such unpleasant sequela.

DR. SCHADEL (Closing).—It was interesting to me that Dr. Paxson noted that 50 per cent of those patients receiving no anesthesia had essentially no pain at delivery. That point interests all of us. We should, therefore, recognize that fact and whatever we give as an analgesic agent should not jeopardize the patient's life. The instance of shock in giving 200 mg. of Demerol intravenously was something I had not experienced in using a dosage of 1 mg. per pound of body weight. I was, unfortunately, not able to see any cases where there was that reaction. In no instance was there any demonstrable cyanosis in infants who had received Demerol and were delivered with pudendal block. However, there were instances of mild cyanosis in infants who were delivered under barbituric acid derivatives with nitrous oxide and oxygen. The nerve which Dr. Grove so adequately described was inadvertently blocked when the skin wheal was raised on the perineum.

HYALURONIDASE IN TREATMENT OF HUMAN STERILITY*

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IN A recent report, Kurzrok, Leonard, and Conrad[1] announced the use of bull testis hyaluronidase in the treatment of certain types of relative human sterility, reporting favorable results in six couples.

Hyaluronidase, an enzyme belonging to the group of so-called "spreading factors," is a component of normal spermatic fluid. It is said to be capable of bringing about the dispersion of the follicle cells surrounding recently ovulated ova of certain mammalian species by its property of breaking down intercellular cement substance, thus making possible the penetration of the ovum by the sperm.

Literature

The background for the therapeutic use of hyaluronidase in human sterility, as well as an introduction to its chemical relationships, has been outlined by Kurzrok et al.[1]

Briefly, the steps leading to the application of the enzyme hyaluronidase to the problem of human sterility may be shown as follows:

1. The demonstration of McClean and Rowlands,[2] and also by Fekete and Duran-Reynals,[3] later confirmed by Leonard and Kurzrok,[4] that hyaluronidase possesses the property of dispersing the follicle cells of the corona radiata of mammalian ova. This removal of the cells surrounding an ovum is apparently a prerequisite to penetration of the ovum by a sperm.

2. The successful attempts by Rowlands[5] to accomplish fertilization in rabbits with artificial insemination by the addition of hyaluronidase to sperm samples ordinarily numerically inadequate to produce fertilization.

3. The finding of Werthessen et al.,[6] corroborated by Kurzrok's group, that, usually, there is a direct relationship between sperm numbers and hyaluronidase content of human semen.

4. The impression, shared by many workers in the field of human sterility, that, in couples wherein the husband's spermatic fluid is mildly deficient, the failure to conceive must be due to something more than merely diminished mathematical chances of a union between an ovum and a sperm.

In the study of Kurzrok and his colleagues referred to in the first paragraph, it is stated that hyaluronidase was used by them by two different techniques. One method involved the addition of 10 to 20 mg. of bull testis hyaluronidase to seminal fluid used for artificial insemination. The other method was

*First of three papers on hyaluronidase studies.

that in which 10 mg. of hyaluronidase was packed into the cervix, designedly before coitus. Details were given of six patients in whom pregnancy followed the utilization of the second method. Criteria governing their choice of patients were given. Proof of ovulation was furnished in their cases by endometrial biopsy. Estimation of ovulation time for use of hyaluronidase was carried out by the vaginal smear method of Papanicolaou and Shorr.[7]

It was not made clear in their paper whether these successful cases were six of a larger series by the packing technique or the only ones in which hyaluronidase was used in an effort to overcome sterility. Nor did they give data about relative merits of the two techniques when clinically applied, referring at one time to the packing technique and at other times to artificial insemination.

Present Study

We report herewith our lack of success in the use of bull testis hyaluronidase by the two methods mentioned by Kurzrok. The series consisted of 25 couples in whom a total of 67 trials with the enzyme were carried out.

The following criteria were utilized in a selected number of cases in which we used hyaluronidase:

1. Any or all faults of the female partner had been corrected as far as possible. Endometrial biopsies were resorted to in proof of ovulation.
2. Major faults in the male partner were corrected when possible. Those husbands with subnormal sperm specimens received appropriate treatment. Specimens of seminal fluid might show reduced numbers of spermatozoa, excessive percentages of abnormal forms, impaired motility, or a combination of any or all of the above. Many of the male specimens fell within normal values.
3. Better to evaluate the efficacy of hyaluronidase, therefore, its use was reserved for those couples in whom the ordinary current methods had failed to result in conception. These are the patients for whom, ordinarily, artificial insemination has been reserved, using husband's specimens, chiefly in the belief that some minor mechanical fault might be a factor.

Without making assays of hyaluronidase content of seminal fluid in these cases, we naturally assumed from Kurzrok's work that the specimens might be deficient or lacking in hyaluronidase, and we were encouraged to believe from what he and co-workers had presented, that the addition of hyaluronidase might be a valuable feature of artificial insemination.

Methods

In the early part of the study, artificial inseminations were carried out in a series of patients, using freshly obtained seminal fluid of the husband, collected usually after seven to eight days abstinence. Twenty mg. of bull testis hyaluronidase* was mixed with 1.0 c.c. of the seminal fluid and 0.5 c.c. of the resultant mixture introduced into the cervix. Insemination was performed usually on the first and third days closest to the ovulation period, as calculated by means of

*The bull testis hyaluronidase was provided by Dr. Erwin Schwenk of the Schering Corporation.

rectal temperature readings.[8] In several instances, insemination was possible only once within the ovulation period.

Because of a consistent lack of success, namely, no resulting pregnancies with this method, we then turned to the other method suggested by Kurzrok for the later part of the study. This technique is, as stated above, the packing of 10 mg. of hyaluronidase into the cervix on or about the day of the "ovulation temperature rise," instructing the couple to have intercourse within a few hours. A number of the couples who were treated with the packing technique were among the group previously receiving artificial insemination of seminal fluid with hyaluronidase.

Results

No pregnancies occurred in these 12 couples from artificial insemination, despite the fact that a total of 34 inseminations were practiced.

In only one instance did pregnancy follow a treatment with hyaluronidase, and that in Case 3 (E. J. T.), wherein cervical packing with hyaluronidase was practiced on the eleventh day of the cycle. This patient usually had twenty-six day cycles. She had received two artificial inseminations with hyaluronidase previously without result.

Lest too much merit be attributed to either of these two methods, it is interesting to note that one of our patients who was given artificial insemination with hyaluronidase had a normal menstrual period after the last insemination, and, following that period, became pregnant without any treatment. This couple with primary sterility had been married for eighteen years. We do not attribute this pregnancy in any way to the use of hyaluronidase, but reflected how easily we could have been misled in conclusions, if no menstrual period had intervened.

An interesting sidelight was the reaction experienced by patient No. 18 (W. J.) who, with each of the three cervical packings with hyaluronidase, experienced symptoms which are probably manifestations of an individual sensitivity to the enzyme preparation.

In order to place on record in detail the criteria for cases in this study, charts are submitted herewith. (Table I.)

Summary and Conclusions

1. A certain average amount of hyaluronidase in the seminal fluid is apparently essential for conception. Hyaluronidase is said to act by causing dispersion of the follicle cells surrounding the ovum, a necessary preliminary to the penetration of a sperm.

2. Theoretically, it would seem, in a sterile couple, that the addition of hyaluronidase to seminal fluid not grossly defective, but heretofore ineffective, should be a valuable adjunct in the use of such fluid for artificial insemination.

3. In spite of apparently favorable reports from other investigators, our findings with artificial insemination with hyaluronidase-treated seminal fluid, in a small series of cases, were entirely disappointing, no pregnancies resulting.

4. We are now investigating Kurzrok's second technique, namely direct application of hyaluronidase to the cervix at ovulation time, to be followed by normal coitus.

5. Of 18 couples in whom this latter "packing" technique has been tried, pregnancy has followed in only one instance.

TABLE I. CLINICAL DETAILS OF HYALURONIDASE STUDY

CASE NO.	HISTORY	FEMALE FAULTS AND TREATMENT	REPRESENTATIVE SEMINAL SPECIMEN	INSEMINATIONS OR CERVICAL APPLICATIONS WITH HYALURONIDASE	RESULTS AND REMARKS
1. P. M.	Married 4 yr. Primary sterility. 3 yr. observation.	Severe menstrual cramps. Moderate tubal obstruction.* D. and C. and suspension, 1944. Insufflations, gonadophysin.	July 29, 1946. 90% motility Total count, 1,020,000,000. 14% abnormal.	June 24, 1946, insemination June 26, 1946, insemination July 29, 1946, insemination July 31, 1946, insemination Sept. 30, 1946, insemination Oct. 1, 1946, insemination Dec. 29, 1946, insemination	Negative
2. M. F.	Married 10 yr. Primary sterility. 6 yr. observation.	Endometriosis; cicatricial stenosis of cervical canal. Unilateral salpingo-oophorectomy. Dilatation of stenosis.	May 14, 1946. 90% motility Total count, 35,000,000. 40% abnormal.	June 25, 1946, insemination June 27, 1946, insemination.	Negative
3. E. J. T.	Married 6 yr. Secondary sterility. (1 miscarriage at 2 mo., Feb., 1945). 1 yr. observation.	Retroflexion of uterus. Moderate tubal obstruction. Pessary, insufflations.	June 28, 1946. 70% motility. Total count, 180,000,000. 14% abnormal.	June 28, 1946, insemination June 30, 1946, insemination. Feb. 21, 1947, packing.	Became pregnant when cervix was packed with hyaluronidase, Feb. 21, 1947.
4. E. W.	Married 11 yr. Secondary sterility. (Normal delivery Feb. 26, 1942). 2 yr. observation.	Low B.M.R. Moderate tubal obstruction. Thyroid medication and insufflations. (4 previous artificial inseminations without hyaluronidase.)	Oct. 11, 1946. 90% motility. Total count, 650,000,000. 20% abnormal.	Oct. 11, 1946, insemination.	Negative
5. M. F.	Married 8 yr. Primary sterility. 2 yr. observation.	Moderate tubal obstruction. Insufflations. (3 previous artificial inseminations without hyaluronidase.)	Oct. 18, 1946. 90% motility Total count, 100,000,000. 20% abnormal.	July 12, 1946, insemination Aug. 28, 1946, insemination. Aug. 30, 1946, insemination. Jan. 17, 1946, insemination. Jan. 20, 1946, insemination	Negative
6. J. S.	Married 18½ yr. Primary sterility. 10 yr. observation.	Irregular periods and tubal obstruction, moderate. Heavy folds of vaginal tissue. Insufflations.	June 19, 1946. 40% motility Total count, 492,000,000. 19% abnormal.	July 17, 1946, insemination Oct. 18, 1946, insemination	Became pregnant Nov., 1946, with one period intervening between last insemination and pregnancy

*The term "moderate tubal obstruction" as used in this chart means that passage of gas on tubal insufflation took place at higher than average pressure ranges.

7. D. H.	Married 2 yr. Primary sterility. 18 mo. observation.	Moderate tubal obstruction; narrow cervix. Insufflations, dilatation of cervix (4 previous artificial inseminations without hyaluronidase.)	Oct., 1945. 50% motility. Total count, 16,000,000. 13% abnormal.	Oct. 28, 1946, insemination. Dec. 23, 1946, insemination Jan. 15, 1947, insemination Feb. 14, 1947, insemination. Mar. 31, 1947, packing. Apr. 25, 1947, packing. May 19, 1947, packing.	Negative
8. Y. F.	Married 3 yr. Secondary sterility. (One stillborn infant 2 yr. ago). 18 mo. observation.	Endocervicitis. Low B.M.R. Moderate tubal obstruction. Cautery, thyroid medication, insufflations.	Mar. 25, 1946. 50% motility. Total count, 88,000,000. 25% abnormal.	Oct. 23, 1946, insemination. Nov. 27, 1946, insemination. Jan. 17, 1947, insemination.	Negative
9. F. H.	Married 9 yr. Primary sterility. 2½ yr. observation.	Retrodisplacement. Moderate tubal obstruction. Pessary, repeated insufflations.	"Specimen within normal limits" (report of outside urologist).	Apr. 10, 1947, packing. May 7, 1947, packing. June 2, 1947, packing.	Negative
10. F. C.	Married 6 yr. Primary sterility. 1 yr. observation.	Moderate tubal obstruction. Secondary anemia. Insufflations, and ferrous sulfate	May 8, 1946. 60% motility Total count, 275,000,000. 18% abnormal.	July 24, 1946, insemination July 26, 1946, insemination May 2, 1947, packing. May 29, 1947, packing.	Negative
11. G. P.	Married 9 yr. Primary sterility. 1 yr. observation	Anemia, irregular periods. Ferrous sulfate.	Sept. 9, 1946, 90% motility. Total count, 67,000,000. 22% abnormal.	Dec. 16, 1946, insemination. Dec. 18, 1946, insemination.	Negative
12. K. N.	Married 3½ yr. Primary sterility. 1 yr. observation.	Small ovarian cyst. Cervicitis. Moderate tubal obstruction. Tubal insufflations, cauterization of cervix.	Oct. 12. 1946. 85% motility Total count, 225,000,000. 24% abnormal.	Jan. 8, 1947, insemination. Jan. 10, 1947, insemination. Feb. 5, 1947, packing. Mar. 5, 1947, packing.	Negative
13. R. N.	Married 1½ yr. Primary sterility. 1 yr. observation.	Cicatricial stenosis of cervical canal. Low B.M.R. Moderate tubal obstruction. Dilatation, thyroid medication, insufflations.	Apr. 29, 1946. 100% motility Total count, 370,000,000. 18% abnormal.	Apr. 14, 1947, packing.	Negative
14. A. H.	Married 16 yr. Primary sterility. 6 mo. observation.	Retroflexion of uterus. Low B.M.R. Moderate tubal obstruction. Pessary, thyroid medication, ferrous sulfate, insufflations.	May 7, 1947. 70% motility. Total count, 40,000,000. 19% abnormal.	May 18, 1947, packing.	Negative
15. L. S.	Married 6½ yr. Primary sterility. 1 yr. observation.	Low B.M.R. Subserous fibroids. Thyroid medication, myomectomy.	June 11, 1947. 90% motility Total count, 75,000,000. 20% abnormal.	May 22, 1947, packing.	Negative
16. R. E. H.	Married 3 yr. Primary sterility. 2½ yr. observation.	Low B.M.R. Moderate tubal obstruction. Thyroid medication, repeated insufflations.	Aug. 10, 1946. 95% motility Total count, 320,000,000. 14% abnormal.	Apr. 14, 1947, packing. May 13, 1947, packing. June 6, 1947, packing.	Negative

TABLE I.—CONT'D

CASE NO.	HISTORY	FEMALE FAULTS AND TREATMENT	REPRESENTATIVE SEMINAL SPECIMEN	INSEMINATIONS OR CERVICAL APPLICATIONS WITH HYALURONIDASE	RESULTS AND REMARKS
17. P. V.	Married 16 yr. Primary sterility. 2½ yr. observation.	Moderate tubal obstruction. X-ray Skiodan acacia shows patency. Repeated insufflations.	July 23, 1947. 75% motility. Total count, 154,000,000. 14% abnormal.	Apr. 21, 1947, packing. May 14, 1947, packing. June 16, 1947, packing.	Negative
18. W. J.	Married 17 yr. Primary sterility. 1 yr. observation.	Low B.M.R. Thyroid extract.	Mar. 29, 1947. 95% motility. Total count, 385,000,000. 15% abnormal.	Apr. 4, 1947, packing. May 2, 1947, packing. May 28, 1947, packing.	General malaise, vulvovaginal itching, burning, abdominal aching and cramping, coughing, and sneezing, and lachrymation after each treatment.
19. W. T.	Married 6 yr. Secondary sterility. (One child, July, 1944.) 6 mo. observation.	Low B.M.R. Thyroid medication.	Jan. 24, 1947. 50% motility. Total count, 600,000,000. 17% abnormal.	May 22, 1947, packing.	Negative
20. J. C. M. K.	Married 15 yr. Secondary sterility. (One child, June, 1934.) 10 yr. observation.	Irregular periods. On Gonadophysin.	May 5, 1947. Total count, 285,000,000. 19% abnormal.	May 22, 1947, packing.	Negative
21. C. D.	Married 5 yr. Primary sterility. 2 yr. observation.	Moderate tubal obstruction. Repeated tubal insufflations.	Feb. 28, 1947. 95% motility. Total count, 1,050,000,000. 20% abnormal.	June 9, 1947, packing.	Negative
22. J. P. W.	Married 4½ yr. Primary sterility. 4 yr. observation.	Low B.M.R. Moderate tubal obstruction. Repeated tubal insufflations.	Mar. 18, 1947. 50% motility. Total count, 60,000,000. 33% abnormal.	June 10, 1947, packing. June 12, 1947, packing.	Negative
23. R. J. F.	Married 7 yr. Primary sterility. 18 mo. observation.	None.	Mar. 1, 1947. 95% motility. Total count, 20,000,000. 27% abnormal.	Apr. 10, 1947, packing. May 12, 1947, packing.	Negative
24. J. F. R.	Married 6½ yr. Primary sterility. 3 yr. observation.	Retrodisplacement. Moderate tubal obstruction. Low B.M.R. Pessary, repeated insufflations, thyroid medication.	Nov. 13, 1946. 15% motility. Total count, 20,000,000. 27% abnormal.	Feb. 10, 1947, insemination. Mar. 14, 1947, insemination. Apr. 4, 1947, packing. May 6, 1947, packing.	Negative
25. D. S.	Married 2 yr. Primary sterility. 6 mo. observation.	Moderate tubal obstruction. Repeated insufflations.	Apr. 4, 1947. 60% motility. Total count, 60,000,000. 43% abnormal.	June 4, 1947, packing.	Negative

6. The lone favorable result in twenty-five sterile couples treated with hyaluronidase would suggest that recent reports on the use of this enzyme in the treatment of human infertility are overoptimistic.

7. The study on which this preliminary report is based, is being continued in other phases.

George H. Fetterman, M.D., Director of Laboratories, St. Margaret Memorial Hospital, initiated and has directed the details of this, the first of a short series of studies on this subject.

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POLIOMYELITIS IN PREGNANCY

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FEW cases of poliomyelitis in pregnancy have been completely reported. Most reports are of isolated cases or of small series.[1-44] The most extensive review of these was made by Weaver and Steiner[45] in 1944, covering 75 cases. The following case is the first one reported with virus and histologic studies on both mother and fetus. The accompanying review summarizes all available case reports of poliomyelitis in pregnancy in the American, English, French, German, and Scandinavian literature.

Case Summary

Patient was a 24-year-old para i, grav. ii, in the eighth month of pregnancy. Prenatal course, as well as entire past history, was not remarkable. Six days before entry into the hospital she became nauseated and vomited. During the following five days she experienced malaise, weakness, anorexia, and constipation. She continued to vomit sporadically. There were aches in her back, neck, sides, and legs, and a persistent temperature of 100.5° F. At time of entry, June 18, 1946, temperature was 102.2° F., pulse 130, respirations 26, blood pressure 115/75. Patient was weak and nervous. Neurological and physical examinations were negative. Red blood cells, 3.4 million, hemoglobin, 10.5 Gm., white blood cells, 11,400, with normal differential. Urine showed 2+ albumin, many fine and coarse granular casts, and 2 to 4 pus cells per high dry field. Fetal heart sounds were present.

Patient was given intravenous fluids, morphine for pain, and oxygen for dyspnea. On the third day after entry there was marked weakness, moderate nuchal rigidity, paralysis of internal rectus muscle of the right eye, and nystagmus of the left eye to lateral gaze. Water was regurgitated through the nose, and breathing was shallow. Spinal puncture showed a pressure of 360 mm. of water, with 200 cells, mostly lymphocytes. Penicillin and prostigmine were started. Fetal heart sounds were still present. Within sixteen hours the weakness became more marked, air hunger was present, and patient would not respond to external stimuli. The extremities were flaccid. Heart sounds were good. Patient was placed in a respirator, and nasal oxygen continued. Within 20 minutes the posterior pharynx began to fill with mucus; patient became cyanotic and pulse could not be felt. She was pronounced dead 62 hours after admission.

Autopsy Findings

Autopsy performed two hours after death revealed signs of asphyxia, a pregnancy of eight months, and evidence of an encephalomyelitis. The cerebrospinal fluid was cloudy, and the leptomeninges were markedly congested. Scattered areas of congestion were present throughout the subcortical white matter, basal ganglia, and brain stem. The anterior horns of the spinal cord were swollen and congested. Microscopically, there was typical perivascular infiltration by mononuclears and occasional neutrophilic polymorphonuclears. In focal areas in the parietal cortex, basal ganglia, cerebellum, pons, and medulla, neurons showed swollen cell bodies, clumping of Nissl substance, loss of nuclear detail, satellitosis, and neuronophagia. Similar changes were present in the spinal cord, particularly in the region of the anterior horns.

Examination of the gravid uterus revealed a well-developed and well-nourished fetus weighing 2750 Gm. and measuring 48 cm. in crown-heel length. Maceration was not present. Scattered petechiae of serosal surfaces were the only gross abnormalities. Multiple sections of cerebrum, cerebellum, brain stem, and spinal cord revealed no abnormalities microscopically.

Through the courtesy of the Hooper Foundation of the University of California, virus studies of brain and spinal cord of both mother and fetus were performed. Poliomyelitis virus was isolated from the maternal tissue, but could not be demonstrated in the fetus.

Discussion

An analysis of 170 cases (case reported here included) of poliomyelitis in pregnancy was made. This includes practically all of the cases reported, with the exception of those analyzed by Aycock[46] only with regard to the stage of pregnancy and sex of fetus. Many of the cases included here have been reviewed in part in previous reports.

In 150 instances, the age of the mother is stated. In Fig. 1, with consideration of the sources from which the material is drawn, it is shown that there is no significant variation from the expected normal age incidence of pregnancy.

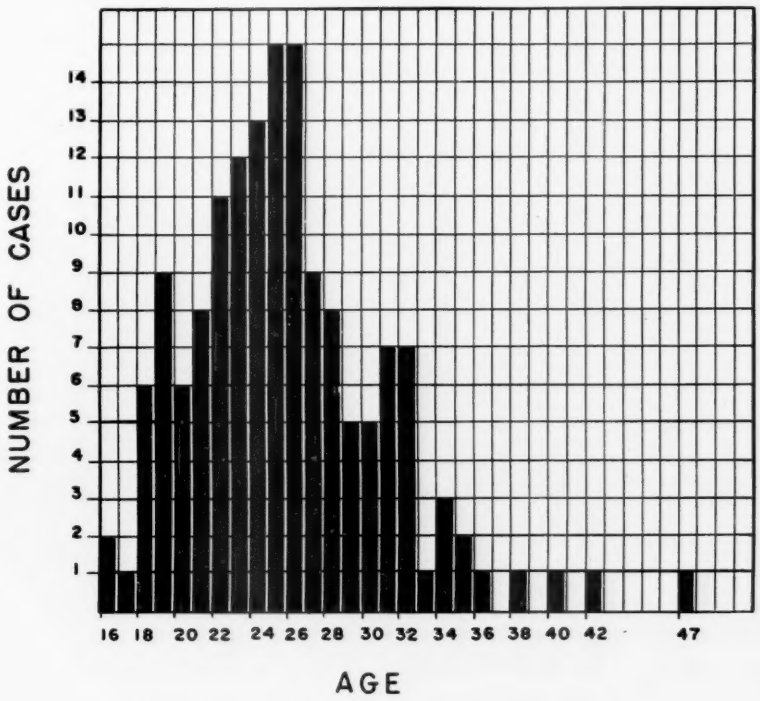

Fig. 1.—Age distribution.

There are 56 instances in which the number of previous pregnancies is stated. Fig. 2 shows no significant variation from the expected normal, the majority being cases of first or second pregnancy.

In 1941, Aycock[27] stated that data collected by him from 56 cases suggested a slight tendency for poliomyelitis to occur more frequently in the last trimester. Weaver and Steiner[45] in their review of 75 cases showed fewer cases to occur in the first trimester. Their animal experiments likewise supported this view. In

1946, Aycock[46] stated that there appeared to be no tendency for poliomyelitis to occur at any specific period of pregnancy. In 166 of the cases reviewed here, the stage of pregnancy is listed. Analysis shows the following incidence:

First trimester	22 per cent
Second trimester	35 per cent
Third trimester	40 per cent
Post partum	3 per cent

This again suggests increased resistance in the first trimester. However, analysis by months reveals that the incidence in the third month is second only to that in the ninth month (Fig. 3). Apparently the low incidence recorded in the first trimester is due to incomplete reporting, or failure to recognize pregnancy in the first two months.

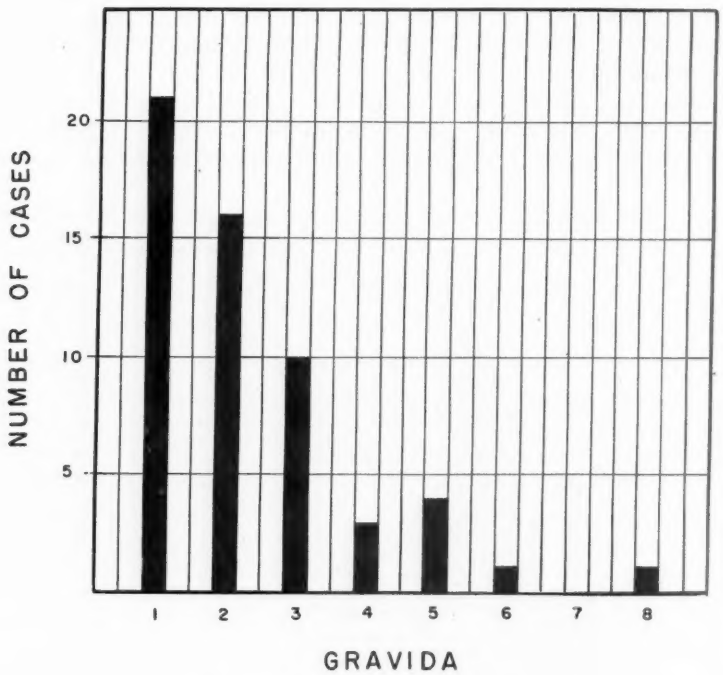

Fig. 2.—Number of pregnancies.

It is now recognized that epidemics vary as to attack rate, incidence and severity of paralysis, and type of paralysis. As early as 1913 Wickman[9] estimated that 25 to 56 per cent of cases of poliomyelitis were nonparalytic, and 6 per cent were bulbar in type. Analyses of recent epidemics show great variation around these general estimates.[47-49] Most data, however, disregard sex and age, and do not allow for comparison with the cases reviewed here. Of these 170 cases, the following is the incidence of type involvement:

Bulbar	23 per cent
Spinal	37 per cent
Aparalytic	8 per cent
Not reported	32 per cent

It is felt that the 23 per cent incidence of bulbar paralysis here is probably higher than the average incidence of such involvement in adult females in epidemics of poliomyelitis.

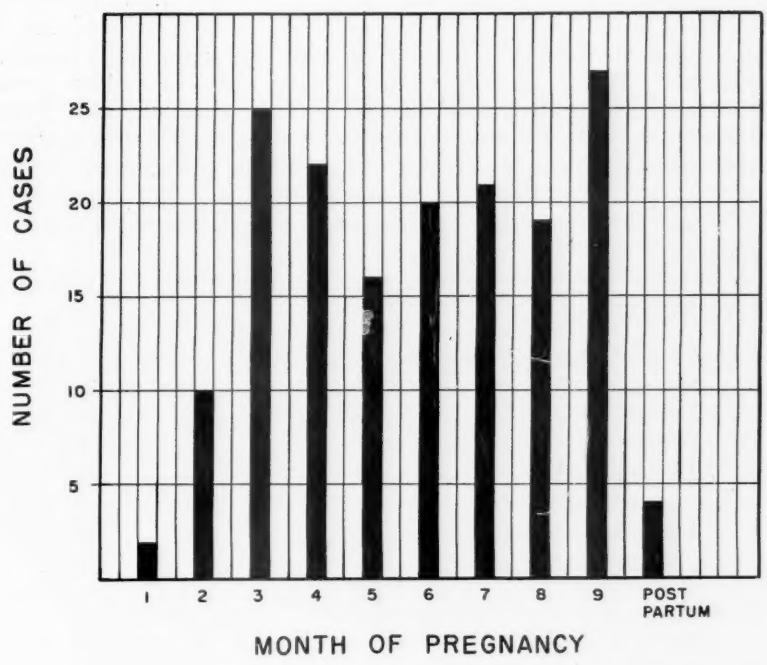

Fig. 3.—Stage of pregnancy

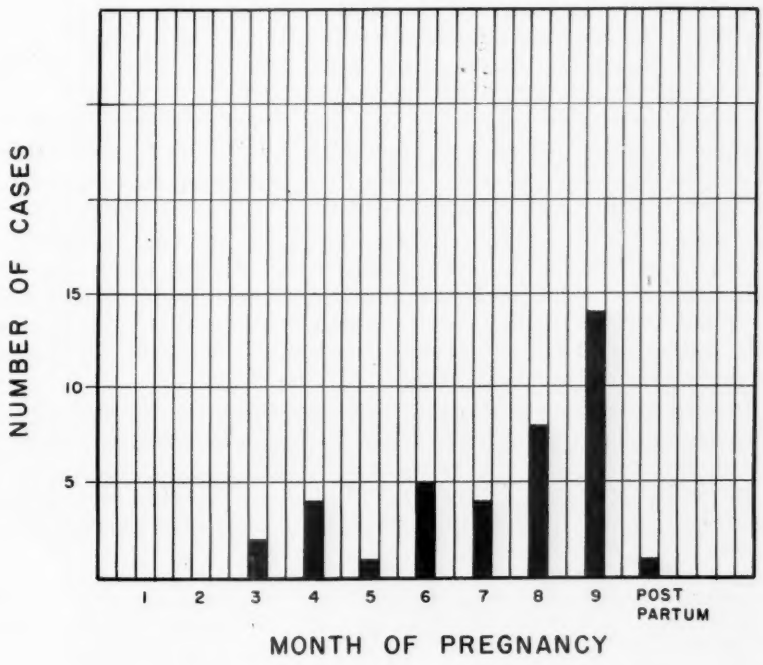

Fig. 4.—Bulbar cases by stages of pregnancy.

Investigation of the 39 bulbar cases shows a marked increase in incidence in the last two months of pregnancy (Fig. 4). An explanation of this fact may lie in the increased mechanical difficulty of respiration normally found in pregnancy. This extra load may either make latent cases of bulbar paralysis apparent or increase the respiratory difficulty in frank bulbar cases. Strauss and Bluestone[43] report a case of a pregnant woman maintained in a respirator from the fifth to the eighth month of pregnancy. With the progress of the pregnancy, it was noted that both the rate and pressure of the respirator had to be increased to compensate for the increasing resistance to diaphragmatic motion produced by the enlarging uterus.

Fetal deaths are reported in 45 instances (26 per cent of cases) and show the following groupings:

1. Type of Maternal Paralysis	
Spinal	15
Bulbar	14
Aparalytic	4
Not reported	12
2. Type of Fetal Death	
Spontaneous abortion	13
Therapeutic abortion	1
Prematurity	3
Stillbirth	7
Cesarean section	6
Undelivered (maternal death)	14
Not reported	1

Nine of the 13 abortions occurred in cases of spinal type paralysis and 3 in aparalytic cases. In one case, the type of paralysis is not reported. Of the 7 premature births, 3 occurred in cases of spinal type paralysis, 1 in bulbar, and 3 in cases in which the type of paralysis is unreported. None of the cases showing bulbar involvement aborted. Only one bulbar case delivered prematurely.

No maternal deaths are reported associated with premature births. This, together with the low incidence of premature births in bulbar cases, suggests that precipitous delivery seldom occurs during an anoxic or agonal period.

Thirty-two maternal deaths, a mortality of 19 per cent, are reported. Of these, 26 showed bulbar involvement, and, in the other 6 cases, the type of involvement is not stated. In the first group, cesarean section (7 cases) may have caused or contributed to death. In the second group, with unreported type of involvement, only one cesarean section was done. The other five deaths were most likely due to respiratory paralysis.

According to numerous authors,[14, 21, 25, 35] respiratory paralysis in the latter months of pregnancy is an indication for cesarean section, not only to obtain a viable child, but to relieve the respiratory distress of the mother. Yet there have been no series of cases of this kind published. In this series, there are 17 cesarean sections reported. The type paralysis, and effect on mother and fetus are as follows:

TYPE PARALYSIS		MATERNAL DEATH	FETAL DEATH
Spinal	2	0	1
Bulbar	9	7	2
Not reported	6	1	3
	17	8	6

All 6 deaths of issue occurred in the fifth to eighth month of gestation. All 7 of the babies delivered by cesarean section during the ninth month and 2 of the 4 delivered during the eighth month lived.

Several authors[20, 50-54] have recorded postnatal findings which are very questionably poliomyelitic in nature, and in which there is no definite proof of poliomyelitis being transmitted from mother to fetus in utero. However, poliomyelitis may be acquired by the newborn infant. Bierman and Pisczek[37] report a case of poliomyelitis in an 11-day-old infant, the mother having shown signs of poliomyelitis twenty-four hours antepartum. Aycock[27] reports the apparent transmission of poliomyelitis, contracted by the mother at term, to a 12-day-old infant. A case reported by Palmstierna[39] is particularly worthy of note. The mother died from poliomyelitis during cesarean section. The apparently normal child showed signs and spinal fluid findings of poliomyelitis twelve days postpartum. Since the child had no contact with the mother, this case is advanced by the author as a possible example of intrauterine transmission of the disease. However, the late development of poliomyelitis in the child suggests an extrauterine transmission.

In all the cases studied in this review, no definite clinical evidence of intrauterine transmission of poliomyelitis has been found. This does not necessarily mean that the placenta acts as a barrier against such transmission. In man, the poliomyelitis virus has been isolated from the blood stream in only one instance.[55] Hence the placenta is rarely, if ever, exposed.

Careful postmortem studies of both mother and baby have been reported in only a few instances. Harmon and Hoyne[34] reported a case in which virus studies on the spinal cord of the fetus were negative. In autopsy on two undelivered maternal fatalities, Waaler[42] found no histologic evidence of poliomyelitis in the central nervous systems of the fetuses. The case presented here showed maternal poliomyelitis by histologic and virologic studies. There was no evidence of poliomyelitis in the fetus demonstrable by either means.

Summary and Conclusions

1. An analysis of 170 cases of poliomyelitis in pregnancy is presented.

2. The age, number of previous pregnancies, and stage of pregnancy do not appear to be factors in the susceptibility of the pregnant woman to poliomyelitis.

3. Bulbar type of paralysis shows an incidence of 23 per cent. The incidence of bulbar involvement is increased in the last trimester of pregnancy.

4. Bulbar poliomyelitis shows no tendency to result in abortion or premature birth, or to cause precipitous delivery.

5. A maternal mortality of 19 per cent and a fetal mortality of 23 per cent is reported. One-third of the fetal deaths were intrauterine and undelivered, associated with maternal death.

6. Cesarean section offers a good opportunity to obtain a viable child, when death of mother is imminent.

7. Poliomyelitis may be transmitted to the newborn, but there is no definite clinical, histologic, or virologic evidence of its transmission in utero.

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MENSTRUAL DYSFUNCTION DUE TO EMOTIONAL FACTORS

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AMENORRHEA and abnormal bleeding constitute two of the most frequently encountered symptoms in gynecologic practice. Evidence has accumulated within the past decade to suggest that menstrual abnormalities may be caused not only by organic, but also by emotional factors, and that, when the latter are primary, surgery and endocrine treatment are often useless. In such cases, therapy must be directed to the cause rather than to the symptoms; in other words, the person presenting the abnormality of menstruation, rather than her organs, becomes the object of therapy.

Ten years ago, a young woman whose persistent metrorrhagia apparently warranted hysterectomy was seen by one of us. However, before operation was undertaken, because emotional upset was evident, an internist was called in consultation. After three hours of conversation, during which anxiety was uncovered and to some extent relieved, the uterine bleeding, which had persisted almost continuously for nine months, ceased. No operation was performed. The patient had no significant menstrual difficulty thereafter, and a follow-up of over nine years constitutes the basis for this report.

In the light of this experience, it has been thought important to review the physiology of menstruation, with emphasis upon those menstrual abnormalities which may be caused by anxiety or other emotional disturbance. In order to avoid destructive surgery in unsuitable cases, the physician must be able to consider in his diagnosis all possible causes of abnormal uterine bleeding, the psychologic, as well as the "functional," and the organic.

Case Report

A twenty-six-year-old single white woman was seen Dec. 12, 1935, for uterine bleeding, then of five months' duration. The family and past history were noncontributory. The periods had started at thirteen, and had always been profuse and irregular. The patient bruised easily with trauma, and had bled once for twenty-four hours, following a dental extraction. There was no history of purpura. The diet was adequate, including fruit, vegetables, and meat. Thyroid medication had been begun in 1932 and was continued during the entire period of observation.

Examination showed a girl of dark complexion and normal hair distribution. No petechiae. Tourniquet test negative. Ocular fundi negative, visual fields full. Breasts virginal, shotty, suggesting cystic disease. Blood pressure 135/80, heart and lungs normal. Abdomen, midline scar, spleen not felt. Pelvic, clitoris normal, fundus forward, endocervix 2.5 cm., whole uterus 8 cm. Unclotted blood coming from a normal external os. Ovaries palpable, normal size.

X-rays showed a small sella with heavy clinoids, thought to be "within normal limits." Metabolism minus 10 per cent. Urine normal. Red Blood count 4.5, white blood count 6.8, hemoglobin 104 per cent (Sahli), platelets high normal; differential leucocyte count normal,

reticulocytes 0.4 per cent; clotting time: (1) 10 minutes, (2) 8 minutes; bleeding time 1¾ minutes; glucose tolerance, fasting, 88 mg., one-half hour, 159 mg., one and one-half hours 198 mg., two hours, 88 mg.; blood Hinton negative.

Abnormal bleeding had begun July 3, 1935, and became so severe that on July eighth a curettement was necessary. (Fig. 1.) Endometrial biopsy showed an estrogen phase. Following curettement (unlike metropathia hemorrhagica) the patient continued to bleed, and bled steadily through July, August, and September, until the third of October, when exploration revealed varicosities of the left broad ligament only. Convalescence from operation was complicated by pain in shoulder and neck and gross hematuria, possibly due to a renal infarct.

Following this operation, she continued to bleed for ten days to October fourteenth. Then, on the eighth of November, she started to bleed again and bled constantly to Feb. 21, 1936. From November thirtieth to December fourth, she received 2,500 units of Antophysin, continued to bleed, and two biopsies, ten and thirteen days following, showed an estrogen type of endometrium. At the time of the biopsies, she was given Antophysin, 2,500 units, and, twenty days after that, still bleeding, had a progesterone type of reaction on endometrial biopsy. Following that, she continued bleeding for over a month, in spite of six doses of Prephysin (anterior pituitary extract) and an additional 2,500 units of Antophysin, this bleeding necessitating a curettement again on February fourteenth. This endometrial specimen showed estrogen influence. The bleeding continued for eight days more, and, on the tenth day following curettement, a secretory type of endometrium was obtained for the second time. This ovulation may have been brought about by curettage, as occasionally happens, but, in spite of this apparently normal period, abnormal bleeding recommenced and continued through the month of March. At the end of March, another biopsy, taken when the patient should have ovulated, showed an estrogen type of endometrium. She was given more Antophysin, continued bleeding, and two more biopsies, nine days apart, at the end of April, showed estrogen phases.

At the beginning of May, she was treated daily with 1 mg. of Proluton, now considered an insufficient dosage, and, at biopsy on the fourth day during the treatment, showed, nevertheless, a secretory endometrium. Her catamenia started five days after this biopsy, and, on the third day of the period, at biopsy, no tissue could be obtained, and the patient's period continued for fifteen days. A Lipiodol examination showed no abnormality of the uterus or tubes. At this point, almost continuous bleeding now having persisted for nine months, the patient and the doctors became discouraged, and it was felt that the uterus should be removed.

It is obvious that a sufficient number of biopsies had not been taken to prove that the patient did not ovulate regularly, but we had proof on two occasions that, in spite of ovulation, her flowing continued abnormally after the secretory phase must have been past. Such bleeding is not typical of the usual metropathia hemorrhagica cases. This fact suggested the advisability of a psychiatric consultation, preliminary to hysterectomy. It is significant that, when the patient was informed that hysterectomy was to be postponed, mild depression and hysterical symptoms for the first time became apparent.

The patient first discussed her personal problems with a physician on May 20, 1936. (Fig. 1.*) Three days later, on May 23, bleeding had ceased. She had normal periods in June and July. The August period was interrupted, but of normal duration. Periods of mild prolonged bleeding then recurred from September, 1936, through April, 1937 (see discussion). For nine years thereafter (May, 1937, to April, 1946) the catamenia have been essentially normal.

Discussion

Menstruation implies cyclic pituitary activity with a chain of consequences, including follicle growth, ovulation, corpus luteum formation, development of a secretory endometrium, and subsequent shedding of this endometrium with bleeding. We know that, given an endometrium under the influence of estrogen, if this hormone be withdrawn, bleeding will occur. Anovulatory bleed-

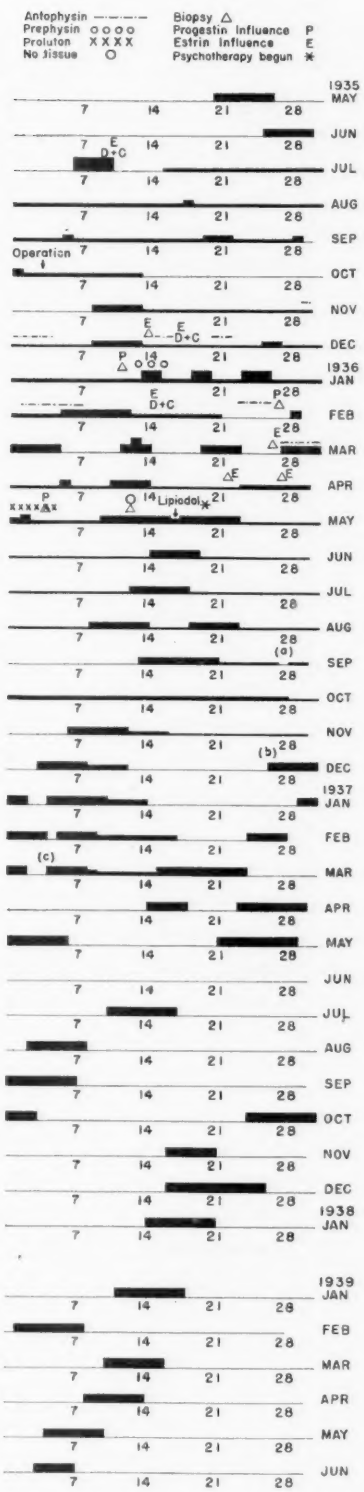
Antophysin
Prephysin
Proluton
No tissue
Biopsy
Progestin influence
Estrin influence
Psychotherapy begun
Operation
Lipiodol
1935
1936
1937
1938
1939
MAY
JUN
JUL
AUG
SEP
OCT
NOV
DEC
JAN
FEB
MAR
APR
D+C
(a)
(b)
(c)

Fig. 1.

ing is of this type. If the endometrium has been previously exposed to both estrogen and progesterone, the withdrawal of the latter hormone alone will result in bleeding. Normal cyclic menstruation involves this mechanism.

Markee[1] studying endometrial transplants in the anterior chamber of the eye, found that, in both ovulatory and anovulatory cycles, there occurs a marked decrease in endometrial volume two to six days before bleeding. This regression, he believes, results from estrogen deprivation. As a result of this tissue loss, buckling and twisting of the coiled arteries take place, with consequent arterial stasis and endometrial necrosis. Just before bleeding commences, there is seen a second vascular change which Markee describes as follows: "Four to twenty-four-hours before the onset of menstrual bleeding there occurs vasoconstriction of the coiled arteries . . . which persists throughout the period of menstrual bleeding, being interrupted in individual vessels only for short periods. It is during these periods of relaxation that menstrual bleeding occurs."

The cause of the vasoconstriction is not known. Smith and Smith[2] have found in menstrual blood a toxic protein believed to result from the products of endometrial catabolism. They say, "the primary cause of endometrial catabolism is certainly hormone deprivation, and the final precipitating factor resulting in flow . . . may well be the above-described atypical euglobulin whose pathological effect is characterized by vasoconstriction, increased capillary permeability, edema, hemorrhage, and necrosis." Markee[3] is in substantial agreement with this hypothesis, postulating the presence of "some substance similar to the necrosin of V. Menkin"—to account for alternating vasoconstriction and hemorrhage.

In metropathia hemorrhagica, bleeding proceeds from a proliferative endometrium, often hyperplastic because of prolonged estrogen stimulation, uninterrupted by ovulation and consequent progesterone influence.* In this condition, the endometrium may outgrow the available supply of estrogen, a consequent relative estrogen deficit resulting, with effects comparable to those following estrogen withdrawal. In metropathia, bleeding ceases following the removal of the proliferative endometrium surgically (by curettage), or medically, by carrying the endometrium into an early secretory phase by means of injections of progesterone, after which it is shed spontaneously.

The cause of the cyclic activity of the pituitary essential to normal ovarian function is unknown. Smith and Smith[4] suggest that the toxin, which, they believe, results from the products of endometrial catabolism, may function as a physiologic stimulus to pituitary activity. They suggest that, since more "toxin" is liberated from secretory than from proliferative endometrium, in metropathia insufficient pituitary stimulation occurs, with consequent low follicle-stimulating hormone production and failure of ovulation. Thus a vicious circle would be set up.

A number of factors are recognized which may interfere with the activity of the pituitary, with consequent disturbance to the menstrual cycle. Thus, with atrophy or destruction of the anterior pituitary (Simmonds' disease,

*Whenever ovulation is absent over long periods, if estrogen production persists, metropathia may result. In young women, an occasional cause of failure to ovulate is the presence of a congenitally thickened ovarian capsule. Here, mechanical interference with follicle rupture is present. In women near the menopause, follicles may fail to respond (by growth and rupture) to a normal or even increased pituitary stimulus. In either case, long-continued bleeding (metropathia) may result.

Sheehan's disease), by interference with the hypothalamic-pituitary pathways (suprasellar cyst), or with functional inhibition of the basophile cells by estrogens (granulosal-cell tumor, estrogen therapy) or by androgens (arrhenoblastoma), follicle-stimulating hormone falls to low levels, ovulation does not occur, and cyclic bleeding ceases. Grave systemic disease, severe anemia, protein starvation, sudden increases in body weight, and hyperthyroidism may each cause irregularity or disappearance of the menses.

Emotion is known to have an important influence upon menstruation. Markee,[5] observing the arrest of bleeding in endometrial transplants during the late phase of menstruation, says, "Fright at this stage causes, within fifteen to twenty-five seconds, reopening of the arteriole which, for five to fifteen seconds, delivers blood that promptly clots." Fear (as of pregnancy) may delay or suppress a menstrual period. The mechanism of such inhibition is not well understood. Once ovulation has occurred, it would seem that bleeding must generally result from the involution of the corpus luteum about fourteen days later.

According to Loeser,[6] temporary arrest of endometrial development may occur as a result of psychic trauma, the endometrium, in whatever phase, remaining in statu quo following the emotional shock.

Loeser studied four women with histories of regular menstruation, each of whom experienced an "emotional shock" during the aerial bombardment of London. Three were exposed to nearby bomb explosions, the fourth developed acute anxiety concerning a possible pregnancy. In each case, an expected menstrual period was missed. Loeser, obtaining endometrial biopsies during the amenorrheic stage, sent the specimens to Emil Novak, who knew the dates of neither the last menstruation nor of the biopsy. In each case, Loeser says "biopsy specimens showed an endometrium at the stage of development it would normally have reached at the time of the shock, suggesting that the shock caused an immediate arrest of development by interruption of release of the proper (pituitary) hormones." Two biopsy specimens showed proliferative endometrium many days after ovulation should have occurred. Ovulation may well have been delayed in these cases through hypothalamic disturbance (as in Albright's cases, see below). More difficult to explain are two biopsies which were interpreted as early secretory endometrium. Loeser believes this indicates that, if an emotional shock be experienced in the postovulatory phase, the endometrium may neither develop nor regress, but remain static and unchanged over a period of days.*

Young women under the stress of college or undergoing the strain of nurses' training often fail to menstruate over a space of several months. Such women have been studied by Klinefelter, Albright, and Griswold,[7] who find, in many cases, complete absence of active estrogen (no bleeding after progesterone withdrawal, atrophic endometrium on biopsy, atrophic vaginal smears) in spite of a normal follicle-stimulating hormone urinary assay. These cases fall, therefore, neither into the group of pituitary failure (low F.S.H.), nor of ovarian failure (menopause, high F.S.H.). As the ovary will not produce active estrogen when stimulated by F.S.H. alone, but needs also a trace of luteinizing hormone (Greep) in order to secrete active estrogen, Albright suggests that

*If the endometrium was, in fact, postovulatory, it would seem more reasonable to postulate that an ovulation, inhibited by the emotional disturbance, had occurred two or three days before the biopsy specimen was obtained. This would better explain an early secretory phase, (in one case on the thirty-eighth day of amenorrhea) than would the assumption that postovulatory endometrium could persist without change for twenty-four days. In any case, Loeser's observations are of interest and should be repeated wherever cases of delayed menstruation due to anxiety are observed.

these amenorrheic women completely lack luteinizing hormone. Absence of the hypothalamic stimulus which normally brings about the pituitary release of luteinizing hormone is suggested as the probable reason for this type of amenorrhea. Such hypothalamic inhibition is believed to result from emotional factors. Estrogen production and normal cyclic periods usually return following relief of emotional tension.

A number of clinical reports[8-11] have appeared, indicating a relation between psychic disturbance and abnormal menstrual function. Delay or suppression of menses as the result of hypnosis or following "suggestion" has been described (Novak and Harnik, and Miller).

It is, therefore, probable that emotion, by causing changes in endocrine balance, may bring about either amenorrhea or uterine bleeding. A more direct neurogenic control of uterine bleeding may also exist. Soskin et al.[12] have shown that, in certain delayed cycles in otherwise normally menstruating women, bleeding may be induced by the injection of prostigmine. During pregnancy, injection of the drug is not followed by bleeding, nor does such bleeding follow the use of prostigmine in amenorrhea due to gross endocrine disturbance. His observation suggests, since the autonomic nervous system is closely associated with the emotional centers, that integration between psychic activity and uterine physiology may be mediated, not only through hormonal changes, but also by direct neurogenic control of endometrial vascularity.

The significance of the emotions appears to be clear-cut in the case here reported. In the course of the second interview, it was learned that the onset of excessive flow had coincided with a period of acute anxiety and indecision relative to marriage. At that moment, the patient had become convinced that her life problem was insoluble, felt doubtful of her competence as a person, and considered herself a failure. Guilt feelings, taking origin from false parental attitudes and childhood experiences, were expressed and modified by discussion. The patient was "desensitized" to certain concepts.

It is probably significant that a subsequent onset of abnormal bleeding (see Fig. 1, a) began during the week before she started a new and difficult job, when fear of failure and sense of personal inadequacy again became acute. Another period of relatively prolonged bleeding (b) occurred when she again "fell in love"; still another, (c) when she was repudiated by the man who "decided to marry the other girl."

In the nine years subsequent to the termination of psychiatric discussions of a simple type, the periods have been more regular than at any time in the patient's menstrual life. There has been no recurrence of prolonged bleeding. The patient has grown in self-confidence and independence. Responsible positions have been successfully held over this nine-year period.

Conclusion

A woman, aged twenty-six, with uterine bleeding of many months' duration, was studied at both somatic and psychic levels. Despite ovulation (two secretory endometrial biopsies), bleeding continued. Organic cause for metrorrhagia was eliminated. Endocrine treatment and minor surgery were both ineffective. Bleeding terminated after three hours of discussion, during which guilt and anxiety were partially relieved.

Proof is lacking that anxiety caused, or that relief from anxiety terminated, the metrorrhagia. The onset of the bleeding, however, coincided with a phase of acute anxiety. The patient bled almost constantly for nine months, during which time no solution of her life problem was evident to her. The bleeding itself, however, constituted a partial solution, as hysterectomy would also, in part, have solved her problem. She was subsequently followed for nine years, during which no abnormal bleeding has occurred.

It is concluded that cases of prolonged bleeding in young women should be studied at both somatic and emotional levels before destructive major surgery is undertaken.

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UTERINE SUSPENSION*

A Report of Results

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THIS is not a clinical study of the causes of success or failure of uterine suspensions. It is simply a review of our own results with the procedure, as a method of relieving a variety of feminine complaints associated with simple or complicated retroversion of the uterus.

So many similar series have been reported with statistical evidence to support the procedures recommended, that one ought to be able to consider the subject a matter of sound and well-established principles.

Although the 220 operations herewith presented were done by different members of the staff of the University Hospital over a ten-year period, the indications and techniques conform, in general, to the principles thus established. Nevertheless, we have personally felt that the operation is a much abused procedure, and, to prove or disprove our theory, undertook a rather painstaking search of the records, paying particular attention to the postoperative reports of the patients themselves. In evaluating the degree of success or failure of any elective surgical operation, we are always confronted with the human equation. However, since subjective symptomatology is usually a primary consideration in determining the need for surgery, the relief or continuation of the symptoms postoperatively should be an adequate criterion of success or failure.

For simplicity, we have classified the patients, as regards end results, into one of four groups, namely: (1) those who were entirely free of all symptoms as "Excellent"; (2) those who were relieved of some, but not all, of their complaints as "Fair"; (3) those who complained just as bitterly or more so of their various symptoms as "Poor," and, finally, (4) those in which the uterus was found retrodisplaced postoperatively as "Failures."

Since all authorities agree that no single operation is universally applicable, the following general principles guided the choice of procedure:

If the retrodisplacement was due to childbirth, the round ligament suspension was associated with repair of the pelvic floor and, in certain instances, reconstruction of the sacral ligaments.

If the retrodisplacement was due to adnexal disease, some type of round ligament suspension which utilized the heavy medial mascular portion of the ligament was used. The Baldy-Webster technique was employed as a method of correcting associated prolapsed ovaries.

The following table illustrates the type operation selected by the various surgeons:

*Presented at a meeting of the St. Louis Gynecological Society, Oct. 9, 1947.

TABLE I. TYPE OF SUSPENSION

	NUMBER OF CASES
Barrett	74
Simpson	68
Baldy-Webster	36
Gilliam	35
Mayo	5
Kocher	2
	220

In an attempt to determine whether the symptoms should be attributed to the retrodisplacement, preliminary trial with pessary in 62 of the 145 movable retrodisplacements produced relief as indicated in Table II.

TABLE II. RELIEF OF SYMPTOMS WITH PESSARY

EXTENT OF RELIEF	NUMBER OF CASES
Excellent	42
Fair	9
Poor	11

With the view of separating cases with coexisting pathology from the simple, uncomplicated retroversions, in the analysis of our results, our series is divided into the two following groups:

Complicated	121
Uncomplicated	99

The following diagnoses were made concomitantly:

TABLE III. TYPE OF COMPLICATION

	NUMBER OF CASES
Menorrhagia	10
Pelvic inflammatory disease	60
Sterility	2
Myomata	2
Cervicitis	47
Relaxed pelvic floor	29
Varices broad ligament	2
Ovarian cyst	5
Habitual abortion	1
Cervical stenosis	1
Visceroptosis	4
	163

The following operations were done at the same time the uterus was suspended:

TABLE IV. ASSOCIATED OPERATIONS

	NUMBER OF CASES
Sturmdorf	31
Tracheloplasty	9
Cauterization of cervix	6
Conization of cervix	1
Myomectomy	2
Colporrhaphy	26
Salpingo-oophorectomy	16
Dilatation and curettage	63
Adhesiolysis	8
Appendectomy	12
	174

Results

In categorizing our results, 52 cases were deleted because of inadequate follow-up or failure of the recorder to make a definite statement regarding the relief of symptoms. Upon the basis of the classification outlined above, results were as follows:

TABLE V. POSTOPERATIVE RESULTS

COMPLICATED: 116 CASES			UNCOMPLICATED: 52 CASES		
EXTENT OF RELIEF	NO. OF CASES	PERCENTAGE	EXTENT OF RELIEF	NO. OF CASES	PERCENTAGE
Excellent	36	31%	Excellent	13	25%
Fair	31	27%	Fair	2	3.9%
Poor	47	40%	Poor	37	71%
Failures	2	1.8%	Failures	0	0%

Comment

It is evident from the above that almost three-fourths of the patients of the uncomplicated group failed to attain satisfactory results from their operations. Since the therapy is far from a lifesaving procedure and, certainly, not entirely without hazard, it would seem that these results are definitely unsatisfactory. The associated surgical treatment given the complicated group can probably be credited for the better results for that group, in which only 40 per cent failed to attain satisfactory results. To illustrate that this procedure is not innocuous, there were, following surgical correction, three cases of thrombophlebitis, two of wound infections, and two patients developed intestinal obstruction in the course of the follow-up period.

Cursory consideration of these results seems to lead to the conclusion that the majority of retroversion operations are unnecessary. More deliberate study of the many factors involved, the majority of which cannot be outlined in statistical tables, has led us to the more constructive viewpoint of Dannreuther: "(a) Retrodisplacements of the uterus per se do not cause symptoms. (b) The concealed complication in cases of replaceable displacement causing symptoms is passive congestion. The true cause of many symptoms credited to a retrodis-

placement will be found elsewhere. Careful differential diagnosis is of paramount importance. (c) A retrodisplacement may be treated prophylactically, expectantly, palliatively or surgically.''

Conclusions

In brief, it is our opinion, as a result of this study, that:

1. We should differentiate coexisting pathology and treat it first. For example, a healed cervicitis may entirely relieve a patient's sideache and backache and obviate the need for suspending the uterus.

2. Laparotomy is indicated without prior trial with pessary when there is need for appendectomy, myomectomy, or salpingo-oophorectomy, or when there are associated pelvic adhesions.

3. Suspension of the uterus is justifiable when preliminary trial with a pessary effects complete relief of symptoms and the patient will not, for reasons of her own, continue to wear the pessary.

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PHENOLSULFONPHTHALEIN AS A TEST FOR THE DETERMINATION OF TUBAL PATENCY

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THIS is to introduce a test for the determination of tubal patency which is simple, physiologic, and safe.

Phenolsulfonphthalein (PSP)* is instilled into the uterine cavity and, at the end of thirty minutes, the bladder is catheterized. If the urine turns red or pink when alkalinized, the tubes are considered patent; if there is no discoloration, the tubes are considered closed. Based upon animal and human experiments, it was found that PSP is not easily absorbed (if at all) from the normal vaginal mucosa, endometrium, or endosalpinx, but is readily absorbed from the peritoneum. Thus, if the tubes are patent, the PSP will pass from the uterus into the tubes and into the peritoneal cavity where it is absorbed, carried to the kidneys, and excreted, giving rise to a positive test. If the tubes are closed, this will not occur and the test will be negative. The thirty-minute period was chosen for two reasons: (1) PSP was recovered in every instance within twenty-five to thirty minutes when injected into the peritoneal cavity of rabbit does, and (2) if the PSP should be slowly absorbed from the tube or uterus, it would not interfere with the efficiency of the test.

Technique

The vagina and cervix are prepared in the same manner as for an insufflation test or hysterosalpingography. All instruments are sterile. The bladder is emptied and a Graves speculum is inserted into the vagina. The cervix is grasped with a tenaculum and the uterus probed with a uterine sound to determine depth and direction. A cannula (similar to that used with the Jarcho or Rubin apparatus) is filled with PSP solution (12 mg. or 2 c.c. of PSP solution added to 20 c.c. of isotonic saline) and inserted into the uterus, the tip being just above the internal os. The rubber obturator on the cannula fits snuggly against the external os and prevents regurgitation. A 20 c.c. syringe containing the remainder of the PSP solution is inserted into the distal end of the cannula and 10 c.c. of the solution is slowly injected into the uterine cavity. The stop-cock at the distal end of the cannula is turned so that there will be no reflux of the PSP solution. The patient is given a glass of water to drink. Ten minutes are allowed to pass before the cannula is removed, for in that time the PSP solution will have passed through the tubes into the peritoneal cavity. A tampon is placed in the vagina and the patient is allowed to rest flat on the table for another twenty minutes. At the end of this time, the bladder is catheterized and the urine collected in a container. Ten per cent sodium hydroxide is added to the urine. If the urine turns pink or red, the tubes are considered patent; if there is no discoloration, closed.

None of the patients seemed to manifest any difficulty during or after the test. Their only complaints were abdominal cramps similar to those found

*Hynson, Westcott and Dunning, Baltimore, Md.

with tubal insufflation or during hysterosalpingography. One patient (No. 6) became pregnant several months after the test.

Sixteen patients were studied and, in each case, the test was found to be accurate in its determination of tubal patency. (Table I.) In ten cases, the tubes were found to be patent as determined by the PSP test. In three of these cases (Nos. 5, 10, and 15) hysterosalpingography was performed and the patency of the tubes substantiated. Case 15 was quite interesting. In 1946, a Pomeroy sterilization was performed. In 1947, when the PSP was done, the results indicated tubal patency which was confirmed by hysterosalpingography.

TABLE I

PATIENT	PRESUMPTIVE CAUSE OF STERILITY	DYE RECOVERED	INSUFFLATION	HYSTEROSALPINGOGRAPHY	SURGERY
1. M. B.	Oligospermia	Yes			
2. A. L.	Oligospermia	Yes			
3. D. S.	Tubal ligation	No			
4. M. B.	Chronic salpingitis and pyosalpinx	No			Bilateral salpingectomy Hysterectomy
5. M. C.	Oligospermia	Yes		Tubes patent	
6. E. E.	Study incomplete	Yes	Patient became pregnant several months later		
7. M. Z.	Bilateral hydrosalpinx	No		Tubes closed	Right salpingectomy and resection of left tube
	Postoperative	No			
	Postoperative	No	Tubes closed		
8. R. W.	Tubal ligation	No			
9. M. G.	Endocervicitis Huhner tests neg.	Yes		Left tube only patent	
10. M. W.	Sterile since birth of child 15 years before. Probably chronic salpingitis	No			
11. N. B.	Bilateral chronic salpingitis	No			Bilateral resection of tubes
	Postoperative	Yes	Tubes patent		
12. B. K.	Oligospermia	Yes	Tubes patent		
13. R. P.	Oligospermia	Yes			
14. R. M.	Tubal ligation	Yes		Tubes patent	
15. J. P.	Not sterile	Yes			
16. G. D.	Tubal ligation	No			

In seven cases, the tubes were found to be closed as determined by the PSP test. In three of these cases (Nos. 4, 7, and 11) the diagnosis was confirmed by subsequent surgery. In Case 11, a bilateral tubal resection was performed for chronic salpingitis with both fimbriated ends of the tubes closed. Following surgery, the tubes were found to be patent as determined by both PSP and insufflation tests. In the remaining cases, the tubes had been previously ligated and were therefore known to be closed.

Although the number of cases is small, still the accuracy of the test to date has been quite encouraging. Therefore, this preliminary report is being submitted with the hope that others may be struck by the simplicity of the test and the ease with which it can be performed, as well as the economic and safety factors; and, having access to larger groups of patients, that they may be able to substantiate the value of this test. The Rubin insufflation apparatus is not

available to all, and any other method of insufflation using air is so hazardous as to be strongly condemned. The PSP test is neither costly nor dangerous and can be easily performed by all.

I wish to express my appreciation to Dr. William E. Studdiford, Director of the Department of Obstetrics and Gynecology at Bellevue Hospital, New York City, and to the Community Health Center, Alexandria, Virginia, for their cooperation in this study.

Addendum

Since this report was submitted for publication, both Rubin and phenolsulfonphthalein tubal patency tests have been performed on eight additional patients. In each case, both tests were in agreement in that the tubes were found to be patent.

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THE TREATMENT OF ERYTHROBLASTOSIS FETALIS WITH Rh HAPTEN

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ERYTHROBLASTOSIS fetalis, in its more severe manifestations, still challenges the best of scientific knowledge, and sometimes does not respond to treatment. Many reasonably successful treatments have been advocated. Wiener,[10] Levine,[8] Davidsohn,[5] Diamond,[6] and others have consistently recommended the transfusion of compatible Rh-negative blood into the infant, because the negative blood would not be influenced by the maternal antibodies in the child's blood stream. Wiener,[11] and Wallerstein,[9] among others, have been successful with simultaneous exsanguination transfusions. This procedure removes the major portion of the child's Rh-positive cells and replaces them with Rh-negative ones. It is frequently successful, but presents numerous technical difficulties. Darrow and Chapin[4] have advocated the use of compatible Rh-positive blood, on the assumption that favorable results are "due in part to the desensitizing action of the transfused cells, as well as to their oxygen-carrying function." In the nonanemic cases with highly active hemopoiesis, some workers, such as Cappell,[1] advocate the withdrawal of some blood preceding transfusion. No method is without serious drawbacks, because of either its inadequacy or the difficulty of timely application. A different approach to the relief of the condition, which might obviate many of the drawbacks of the previous methods of treatment, should be of interest.

We here present the treatment of a case of erythroblastosis neonatorum, of the edematous, nonanemic type, by the application of a new approach to the subject. The treatment consisted of injections of an active fraction from Rh-positive blood, the separation of which was recently reported by one of us.[2]

Mrs. S., the mother of the baby treated, first came under our observation in 1940, when she was admitted to the hospital in the 36th week of pregnancy, with the diagnosis of abruptio placentae and toxemia of pregnancy. She delivered a macerated male fetus and was transfused with 500 c.c. Group B blood from her husband. She progressed to recovery without difficulty.

The second child, a female, was born in another hospital at the 36th week. A marked icterus was noted on the first pediatric examination. This proved to be progressive. A decision to transfuse the child was made on the second day of life, but she died before the father could be summoned as a donor. A postmortem examination revealed a marked icterus of the tissues, early pulmonary congestion, very marked enlargement and engorgement of the spleen and liver, with marked hemopoietic activity in the stroma of the organs.

The third pregnancy resulted, in February, 1943, again in this hospital, in a girl who is now living and well. Recent examination of her blood showed her to be Group B, Rh negative. This was the last child by the first husband, who was later killed in service. He was Group B, and, by later inference, Rh positive, and heterozygous.

The fourth pregnancy resulted in the erythroblastotic baby girl whose treatment is described. The mother had an uneventful pregnancy, except that her delivery was one month beyond the expected date. During her pregnancy her blood examination showed she is Group B, Rh negative, and, at 32 weeks, showed positive for anti-Rh sensitization with Race's test and blocking antibodies through a 1:40 dilution. The father was shown to be Group A. His cells were negative to the standard (anti-Rho or anti-D) serum, but were agglutinated by the serum of Mrs. S. Further investigation showed Mr. S. to be an Rh″ or cdE type and Mrs. S.' serum contained blocking antibodies of anti-Rho (anti-cDe) specificity and agglutinins against Rh″ or cdE. (This work was checked by Dr. Philip Levine.) It is probable that the first husband provided the stimulus for the formation of anti-Rho (anti-D) blocking antibodies.

The child of this fourth pregnancy was delivered at 7:55 A.M. June 8, 1947, after a four-hour labor. The baby was quite edematous, with considerable mucus which could not be entirely relieved by aspiration, so she was placed in an oxygen hood. Examination one hour after delivery showed marked edema, icterus of the skin and sclerae, enlarged liver and spleen, and considerable moisture in the lungs. She was quite lethargic.

Stained smear of cord blood showed 100 immature red cells for every 100 white cells. There were 6,090,000 red cells, 24,000 white cells (corrected count), hemoglobin 18 Gm. Agglutinins against the child's cells and the father's cells were recovered according to the method previously described by ourselves,[3] and by Haberman and Hill.[7] The child was re-examined six hours after delivery. She was still lethargic, and still had an abnormal amount of mucus; the icterus was about the same as before, but the edema of the face and neck seemed to have increased. An icterus index at this time was 200, and the child's cells were Group B, Rh″ (cdE).

Since the progress seemed to be unfavorable, and since, in our experience, erythroblastotic infants showing marked edema rarely survive, it was decided to treat the child with the Rh-positive blood fraction substance which was kindly furnished by its originator. As reported elsewhere, this substance is apparently a lipid fraction from Group 0, Rh-positive blood, which specifically inhibits anti-Rh agglutinins and appears to be hapten. It has proved to be antigenic in experimental animals only in the presence of a protein carrier. No local or general reaction was noted. The following morning, the edema had subsided to a marked extent, mucus was not noted, and the lungs were clear; icterus was slightly improved. The oxygen hood was removed. At that time the red blood count was 5,900,000; white count, 18,000; hemoglobin, 18 Gm.; 39 immature red cells to 100 white blood cells. No agglutinins were recovered from the child's cells. On this second day, another 50 c.c. containing 200 mg. of the Rh fraction were given intramuscularly. On the third day, all the mucus and edema were gone; the child was eating normally, artificially fed, because the mother's milk contained antibodies. The red count was 5,510,000; white count, 10,000; hemoglobin, 18 Gm.; 12 immature red cells per 100 white cells.

Further progress was relatively uneventful. The child gained normally and was discharged with the mother on the eighth day. At that time the red cell count was 5,270,000; white cell count, 13,700; hemoglobin, 18 Gm.; no immature red cells. Study of the maternal serum, six weeks after birth of the child, showed blocking antibodies in a 1:40 dilution and persistent agglutinins for cdE cells in a titer of 1:64. The child was in excellent condition, apparently normal in every respect.

In summary, we have presented a potentially severe case of erythroblastosis which was treated by the use of the nonantigenic specific Rh fraction with recovery.

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TORSION OF A PREGNANT UTERUS WITH RUPTURE*

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SEARCH of the existing literature has revealed no report of a case of torsion of the pregnant uterus with spontaneous rupture.

Rupture of the uterus per se, due to all causes, occurred, according to Lynch,[1] 44 times out of 41,706 deliveries or an incidence of 1:1;118. Spontaneous rupture, however, occurred only in 5 cases in this series, or an incidence of 1:8,341. Cosgrove[2] found 32 cases in 67,000 live births with a maternal mortality of 34 per cent but makes no mention of spontaneous ruptures. Eastman,[3] in discussing Lynch's paper, cited 53 ruptured uteri out of 53,000 cases or 1:1,000, out of which 17 cases, or 1:3,100, were spontaneous ruptures. At the Chicago Lying-in Hospital there were 37 cases of ruptured uteri in a total of 60,388, of which 16 cases, or 1:3,774, were spontaneous ruptures. (Adair et al.[4]) Spontaneous rupture of the uterus is a comparatively rare phenomenon.

Torsion of the pregnant uterus occurs even more rarely. Most of the standard textbooks on obstetrics make no mention of it. We are here reporting what we believe to be the first case of torsion of a pregnant uterus with spontaneous rupture.

Mrs. H. A., a 36-year-old para i, gravida ii, was admitted to the Unity Hospital on April 13, 1946 at 5:30 A.M. with a history of having been awakened from sleep by pain in the abdomen of a "sticking and cutting" character. This pain did not subside. She complained that the pain was "excruciating and unbearable," and that she did not feel her baby.

Her last menstrual period in this pregnancy was Sept. 17, 1945. She had had one normal pregnancy with spontaneous delivery eight years prior to admission. The past history was otherwise negative. She bled for one day in the 12th and in the eighteenth week of gestation. From the fourth month on, she experienced pain in the left groin and had to sit practically all the time. Throughout the antepartum period, her blood pressure ranged from 110/90 to 120/70, urinalysis negative. Two weeks prior to admission she felt contractions for two days, simulating labor pains. There was no history of a fall or other trauma. There was no history of vaginal bleeding on admission.

The patient was admitted to the hospital in profound shock. The pulse was imperceptible, the blood pressure was zero. The abdomen was tense, the uterus was hard, ligneous, and tetanically contracted. A tentative diagnosis of abruptio placentae with possible ruptured uterus was made. Plasma was started in both arms. Although conscious, she was confused, restless, and dulled in sensorium. In the fifteen minutes required to move her to the operating room, she became

*Read at a meeting of the Clinical Society of the Unity Hospital, April 23, 1947.

deeply comatose with all the signs of rapidly advancing death, i.e., dry corneas, widely dilated pupils, gasping respiration of a slow and irregular rhythm, livid and cyanotic mottling of the thighs and abdomen.

A sternal infusion was started as soon as the patient arrived in the operating room and plasma was injected by syringe. Thereafter, 2,500 c.c. of whole blood were allowed to drip rapidly through the intrasternal needle. The operation was begun without anesthesia.

At operation, a cesarean hysterectomy and a right salpingo-oophorectomy were done. Intra-abdominally there was a considerable amount of free blood. The uterus was enlarged to the size of a full-term pregnancy. There was a torsion of the uterus about its cervicouterine junction of 180 degrees and there was an inverted U-shaped rent in what was supposedly the anterior surface about 2 inches in length but which appeared to be complete. On opening the uterus through this tear, there was a considerable amount of free blood in the uterine cavity. The placenta was completely detached and there was a stillborn female about the size of a 26 to 28 weeks' gestation. The stillborn fetus was extracted and a supracervical hysterectomy and right salpingo-oophorectomy were then performed. On examining the uterus it was found that this tear was on the posterior surface which had presented itself anteriorly.

When the operation had advanced to the point of peritoneal closure, anesthesia was started. The respirations became quicker at that time, regular in rhythm and normal in pattern. The pulse was now 110 and the systolic blood pressure 60. Relaxation was adequate but dilatation of the intestines was marked, requiring and responding to 0.2 c.c. surgical pituitrin injected intrasternally.

Pathological Report.—Uterus enlarged and ovoid in shape; measures 15 by 15 by 7 cm.; right adnexa attached. There is a horseshoe-shaped irregular tear on the posterior surface extending from midline downward, which measures 5 cm. and extends through to the uterine cavity. (Fig. 1.)

A thin-walled cystlike structure, amniotic membrane, protrudes through the internal ring. There is a small protruding nodule from the posterior wall. On section a large sac is seen occupying the endometrial cavity. No embryo or fetus is seen.

Microscopic sections show the uterus to have characteristic hypertrophy of muscle fibers. There is a large vessel suggesting a vein which is filled with a red and white thrombus. There is also a markedly elongated and wide, irregular space which in some places has a lining epithelium which suggests a vein. The lumen of the space contains a plasma and red cell clot with a high proportion of leucocytes imbedded in the clot. There is hemorrhage between the muscle fibers. No evidence of necrosis, the uterine walls show numerous trophoblastic cells invading the myometrium together with a decidual reaction.

Diagnosis.—Hypertrophy of myometrium; extensive venous dilatation and thrombus; rupture of myometrium; uteroplacental apoplexy.

Postoperatively, the patient was given supportive treatment including penicillin and repeated blood transfusions. On April 28, fifteen days after the operation, the temperature rose to 103.8° F. and she complained of severe pain in the right chest posteriorly and right shoulder. Physical examination and x-ray revealed the presence of a pulmonary infarct. Resolution was effected by bed rest, sulfadiazine, and penicillin and the patient was discharged on May 16, 1946, one month after the operation.

There was no external evidence of phlebothrombosis or thrombophlebitis on discharge from the hospital. However, twenty-one days after leaving the hospital, another pulmonary infarct occurred, from which she completely recovered.

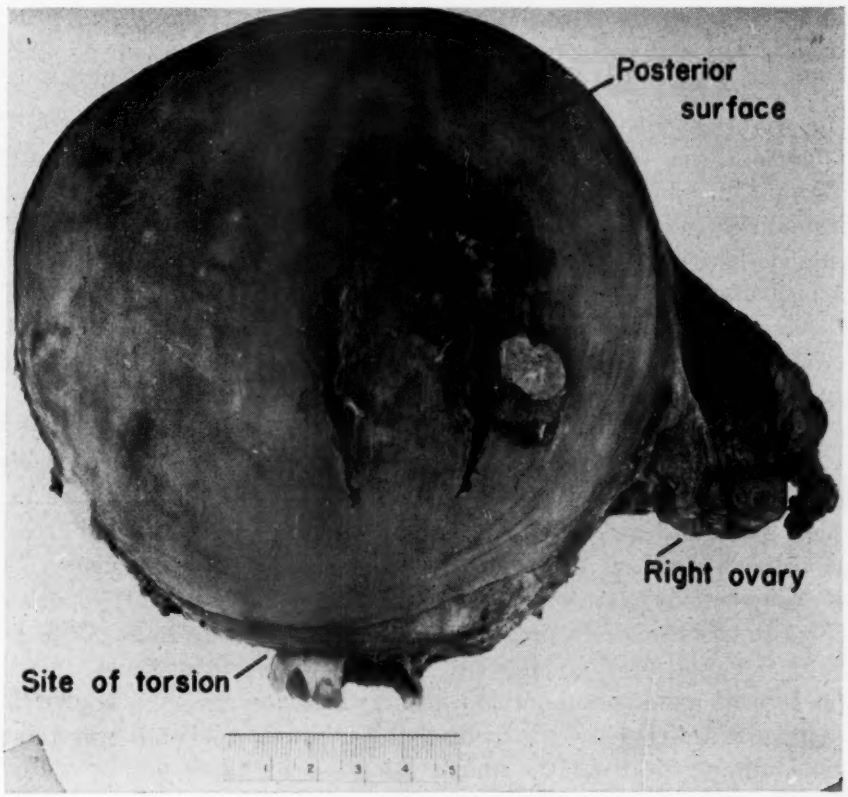

Fig. 1.—Photograph of specimen showing site of rupture on posterior surface of uterus, right tube and ovary, and where the torsion occurred in the cervicouterine junction. At operation the posterior surface of the uterus presented itself anteriorly.

Comment

Primary torsion of the pregnant uterus constitutes one of the rarest emergency conditions of gestation. Its consideration in the differential diagnosis of accidental states in pregnancy has been such that the diagnosis has scarcely, if ever, been made before treatment was instituted. The existence of torsion as a pathologic entity, although known to occur in cattle and other animals, did not appear in the literature of human beings until Virchow[5] recorded it at a postmortem examination in 1863.

During normal pregnancy a certain degree of torsion is present. In 80 per cent of normal cases at term, the pregnant uterus lies slightly dextroverted and twisted on itself from left to right.[6] When the uterus rotates on its axis to a degree enough to cause arrest of circulation in the power pelvis, the torsion produces an acute abdominal syndrome and crisis.

In 1931, Robinson and Duvall[7] summarized twenty-five previous cases of torsion in pregnancy from literature of other European authors from 1894 to

1929, and added one of their own, a case of torsion in a uterus bicornis unicollis in which the patient died unoperated upon and undiagnosed. In none of these cases was there on accompanying diagnosis of rupture of the uterus. Reis and Chaloupka[8] reported what was practically the first case of axial torsion in which the diagnosis was made preoperatively. In their case the torsion occurred in a 25-year-old primipara, at the junction of the cervix and lower segment, and the degree of rotation was 135 degrees. The diagnosis was made when the left round ligament was palpated through a thin abdominal wall as a stretched band running diagonally to the upper right side of the abdomen. At operation no abnormalities were found in the uterus. Day[9] reported two cases of torsion, undiagnosed, in which one was due to a large ovarian cyst and the other to fibroids in a uterus of four months' gestation. A case of 180 degree axial torsion of a gestation of eight months was reported in 1935 in which the etiologic factor was a rigid cicatricial cervix of traumatic origin.[10] Recovery followed cesarean section in this case. Corr[11] reported a case of axial torsion of a gravid uterus in two successive pregnancies. Macleod[12] cited a case of torsion of 180 degrees in a three-month pregnancy in which a hysterectomy was performed. Bell[13] reported a case of torsion in a pregnancy of six months' duration in which the torsion was 180 degrees. The diagnosis was not made but it was recognized as some acute abdominal condition necessitating immediate surgery. An abdominal hysterectomy was performed. Manahan and Coronado[14] reported axial torsion in two cases of early pregnancy associated with myomas. Both had undergone 180 degree torsion and were subjected to hysterectomies. Smith[15] reported a case of axial torsion which occurred during labor in a primipara at term. A cesarean section was immediately performed for what was thought to be an impending rupture of the uterus. In this case there was no maternal or fetal mortality.

Axial rotation of the pregnant uterus, usually clockwise, when viewed from below, may be either to the left or right although the latter is more common. The degree of rotation in most of the reported cases has been from 90 to 360 degrees. A case is reported of a pregnant myomatous uterus in which there was a torsion of 540 degrees.[16] In this case the body of the uterus was necrotic.

Aside from the fact that pelvic tumors such as fibroids, ovarian masses, or adhesions can conceivably cause torsion of a pregnant uterus, the explanation for the spontaneous variety is conjectural. Here transmission of body movements, filling degree of neighboring organs, especially bladder and lower intestines, may play a role. A sudden twist or turn in bed or certain household duties may be the cause. Robinson and Duvall[7] stated that without uterine abnormalities there can be no torsion. They believe that torsion or axial rotation in the absence of tumors or malformations is due to a developmental asymmetry of the uterine musculature.

The case cited above apparently falls into this category for there were no evidences of uterine abnormalities present. The rupture of the uterus probably occurred at the site of the greatest defect in the musculature resulting from the 180 degree axial torsion.

It is to be emphasized that torsion can occur gradually or suddenly and in the latter case the symptoms are more bizarre and constitute the gravest of abdominal crises. Pain in the abdomen in torsion, uncomplicated by rupture (which will undoubtedly confuse the picture still more), usually reveals a tenderness that is not consistent throughout the entire abdomen. It is more marked within the confines of the uterus itself and usually on the side of the torsion.

Review of the literature reveals an important negative finding in cases of torsion in pregnancy, namely absence of vaginal bleeding. This we believe to be characteristic of this rare complication of pregnancy. In our case likewise there was no vaginal bleeding.

Summary

1. A case of torsion with rupture of a pregnant uterus is reported, the first to be cited in the literature.

2. The existing literature of this rare condition is reviewed and an attempt is made to present a symptom complex for torsion.

3. It is emphasized that a diagnosis of torsion in a pregnant woman is rarely made preoperatively. We should add this possibility to our list of differential diagnoses in the emergency states of pregnancy especially where there is no history of vaginal bleeding.

We wish to thank Dr. Barnett A. Greene, attending anesthesiologist of the Unity Hospital, for his anesthetic management of this case; also our thanks to Dr. W. E. Youland, associate pathologist of the Unity Hospital, for his descriptions of the specimen

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OVARIAN DYSGERMINOMA*

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THIS case is being presented because of the rarity of this type of specialized ovarian tumor and because of its uncertain status in regard to malignancy.

F. L., a white woman, 38 years of age, married, was admitted to the Norwegian Hospital on April 8, 1942, (No. 89190) with the following complaints: Mass in abdomen, 7 weeks, frequency of urination, 6 to 7 months, loss of 10 pounds, 1 year, and anorexia and constipation, for an indefinite time.

History.—Essentially negative except for a "nervous breakdown" five years previously and a primary amenorrhea. She had three sisters, all of whom had hypoplasia of the genital organs with sterility. These sisters were born from two different mothers, but all had the same father.

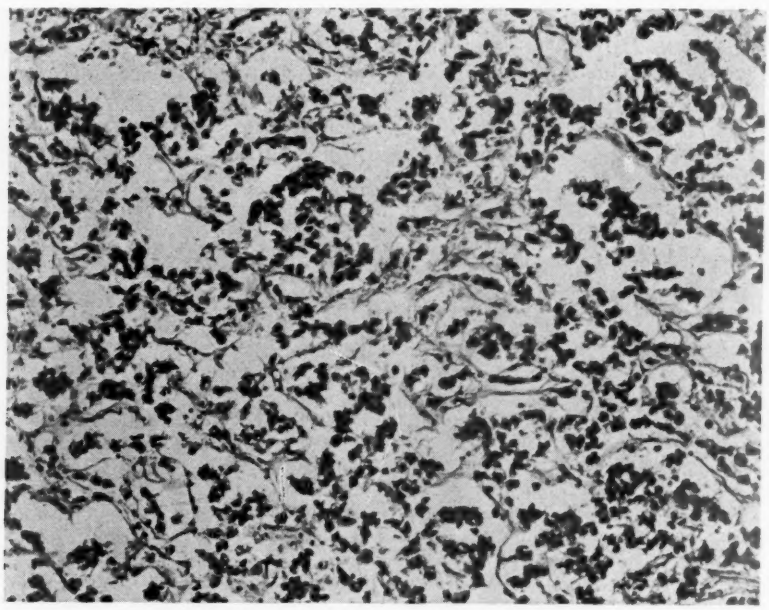

Fig. 1.—Microscopic section of tumor (×140) showing the typical architecture of the ovarian dysgerminoma, with cells arranged in alveoli, and nests with loose fibrous tissue septa infiltrated with lymphocytes.

The patient was fairly well developed and nourished, with dry skin, and in no acute distress. Breasts were poorly developed. Heart and lungs were normal. A nonpainful mass was felt, filling the lower left side of the abdomen.

Pelvic examination revealed hypoplastic external genitals and a small clitoris. The vagina was short, and a small uterus and right ovary were felt. The left ovary was found to be the seat of a large, solid tumor extending from the cul-de-sac to the level of the umbilicus. Parametrium was free.

Blood count, urinalysis, and sedimentation time were normal.

*Presented before the Brooklyn Gynecological Society, June 2, 1943.

At operation, this large, solid tumor of the left ovary, with a dense nodular capsule, was removed intact without difficulty. There were no signs of any extension to the pelvic viscera.

Pathologic Report.—Tumor mass is kidney shaped, measuring 15 by 22 by 10 cm. It is covered by a smooth, dense capsule whose surface is nodular. On cut section, it is grayish-yellow in appearance and of "rubbery" consistency, with numerous areas of punctate hemorrhages.

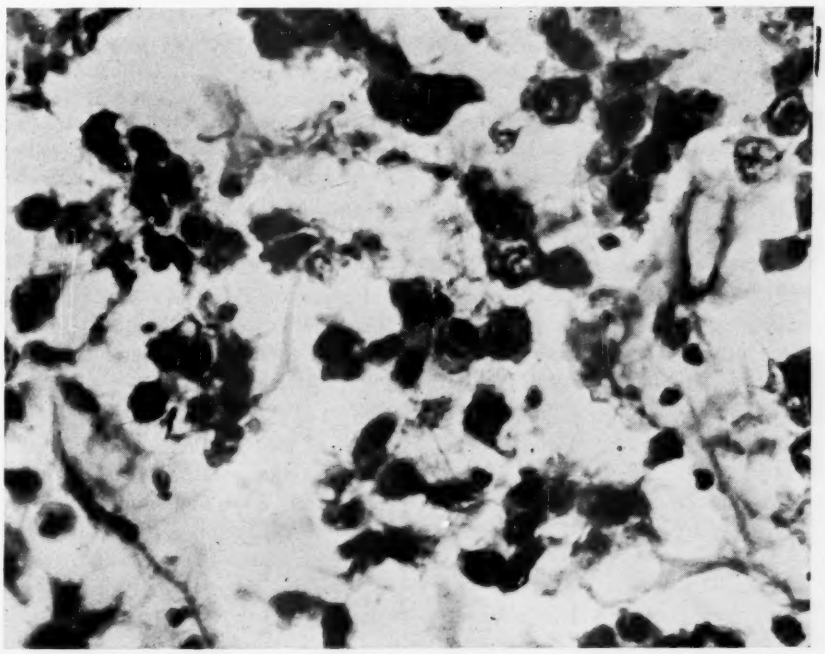

Fig. 2.—Section of tumor (×650) showing the large round or polygonal cells. The cells have large, deeply-staining nuclei, with clear, pale-staining cytoplasm, and show the alveolar arrangement and many mitotic figures. The fibrous tissue septa are infiltrated with lymphocytes.

Microscopic Section.—This shows numerous closely-packed, large round cells with light cytoplasm and large, dark-staining nuclei. The cells are arranged in nests, with thin fibrous-tissue septa infiltrated with lymphocytes. Mitotic figures are seen. The tumor is very cellular with scant fibrous tissue.

Diagnosis.—Dysgerminoma of ovary.

The patient made an uneventful recovery. Six weeks after discharge from hospital she received a course of deep x-ray therapy. She is well to date, and has gained 16 pounds.

544 78TH STREET

TRUE HERMAPHRODITISM*

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TRUE hermaphroditism, requiring for definition the presence of both ovarian and testicular tissue associated with male and female secondary sex characteristics, is an extremely rare entity. Young[6] was able to find but twenty authentic cases, of which only nine were proved microscopically. From time to time additional cases have since been reported. With this presentation, according to Gudernatsch,[3] the thirty-ninth case has been authenticated. Case No. 38 was reported by Halpern[4] before the New York Pathological Society in 1939, but did not receive publication.

Not long ago, I had the good fortune of studying an individual presenting both masculine and feminine characteristics. Investigation at operation and histologic study of biopsied tissue established the case as a true hermaphrodite.

J. H., aged 21 years, first came to me following her sophomore year in college, complaining of primary amenorrhea. Detailed history disclosed that at birth an enlarged penile-like clitoris was noticed. Its amputation was advised, but the parents refused. The patient's childhood was not remarkable until adolescence. Pubic hair developed at the age of 13, and during the following year her parents noted a beginning low-pitched voice and hair development on the upper lip. She was considered a "tomboy" and neighbors commented on her peculiarities. She enjoyed being with boys, playing football and baseball, and avoided companionship of girls. Family difficulties arose over these matters and her preference for wearing boys' clothes. During her late teens she became interested in girls, and on several occasions experienced penile-like erections of the clitoris, causing considerable embarrassment. In recent years she has been conscious of these abnormalities, and of failure of breast development, low pitched voice, and amenorrhea.

On admission to the hospital, examination revealed a 132-pound individual with general body contour and appearance of an adolescent male. Shoulders were broad, hips thin. She had a firm handshake, low-pitched voice, a masculine gait, and masculine carrying angle of the forearm at the elbow. Hair distribution, however, was predominantly feminine with a female type escutcheon and absence of beard, although a definite moustache was present on the upper lip. General physical findings, save for genitals, were normal.

A large penile clitoris was present, measuring 5 cm. in length. The organ was made up of two lateral corpora cavernosa penis, a well-developed prepuce, frenulum, and pseudoglans. A central corpus cavernosum urethra was lacking, thus giving it the appearance of a hypospadic penis with external urethral meatus at its base. Scrotal-like structures replaced the labia and separating these was a normal-appearing vaginal introitus. A vagina with hymenal opening was present, readily admitting one finger. It had a depth of 6½ cm., terminating in an infantile cervix. No testicular tissue was palpable in either scrotal sac nor could testes be found in the inguinal canal.

Routine blood studies, chemistries, and urinalysis were normal. Urine assay for androgenic 17-ketosteroid revealed an excretion of 9 mg. a day, which according to Dubriner was within normal range. Report by Papanicolaou on repeated vaginal smears

*Presented at the meeting of the Minnesota Society of Obstetrics and Gynecology, Minneapolis, Minn., May 4, 1946.

was as follows: "Very scanty exfoliation of epithelial cells. Leucocytes relatively numerous. A few erythrocytes. The endocervical smear contains more cells, mostly cervical. The cytology is suggestive of an atrophic amenorrhea type." X-ray series of the pelvis revealed a pure anthropoid type.

At exploratory operation, the internal pelvic organs were as follows: Present in the midline was an infantile uterus consisting largely of cervix and hence intimately attached to the posterior wall of the bladder. Rudimentary round ligaments, uterovarian ligaments, and tubes were found in normal location. At the lateral terminus of the left uterovarian ligament was found a slightly thickened area, presumably ovary; biopsy was taken. A second biopsy was taken from a corresponding area on the right. Attached to the latter at its medial aspect was a pedunculated gray mass of tissue measuring 2 cm. in diameter. From it biopsy No. 3 was obtained.

Histologic study from the first biopsy revealed it to be typical ovarian cortical tissue of fetal type. No primordial follicles were found. Section of biopsy from the corresponding area on the right disclosed it to be primarily tubular structure of mesonephric origin, interpreted as rete testes. An additional section here also revealed a thin segment of undeveloped ovarian tissue. Biopsy No. 3 proved to be testicular tissue. Scattered primitive seminiferous tubules were recognizable and between these were large areas of interstitial cellular tissue. There was no evidence of neoplastic tendency.

Armed with this information, the matter was discussed at length with the patient during her convalescence. It was her wish to live as a male. Psychiatric consultant also advised that the dominant male characteristics be preserved. Hence, because of the evidence of relatively long-standing masculine tendencies based on a predominance of testicular hormonal tissue, a second operation was performed. At this time all remaining ovarian tissue was removed.

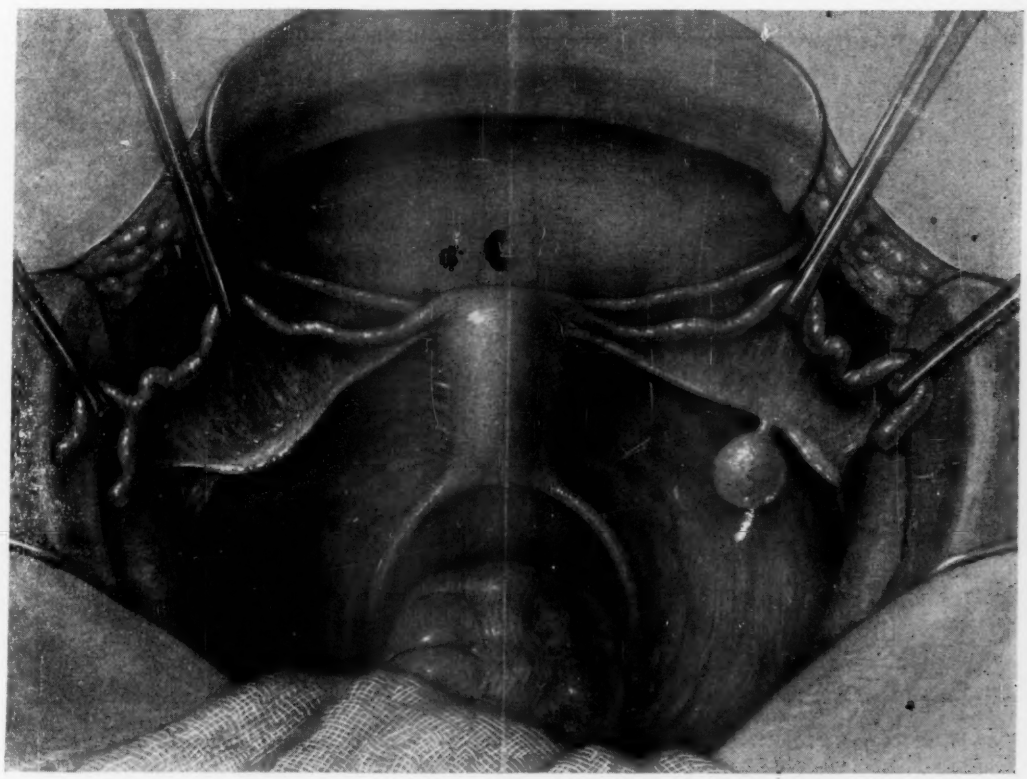


Fig. 1.—J. H. Laparotomy findings in hermaphrodite. Note infantile uterus and tubes, ovarian thickenings bilaterally, and testis on right.

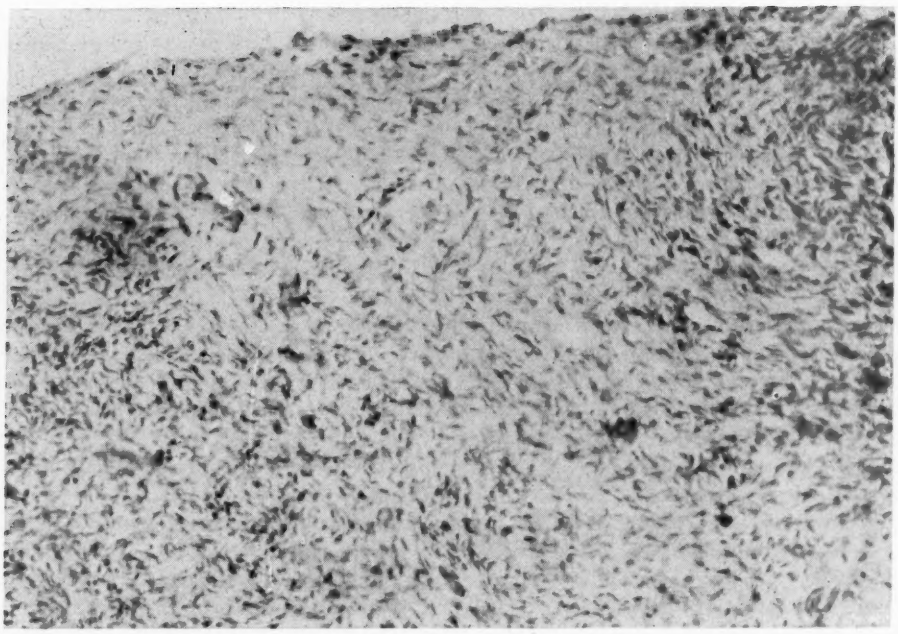
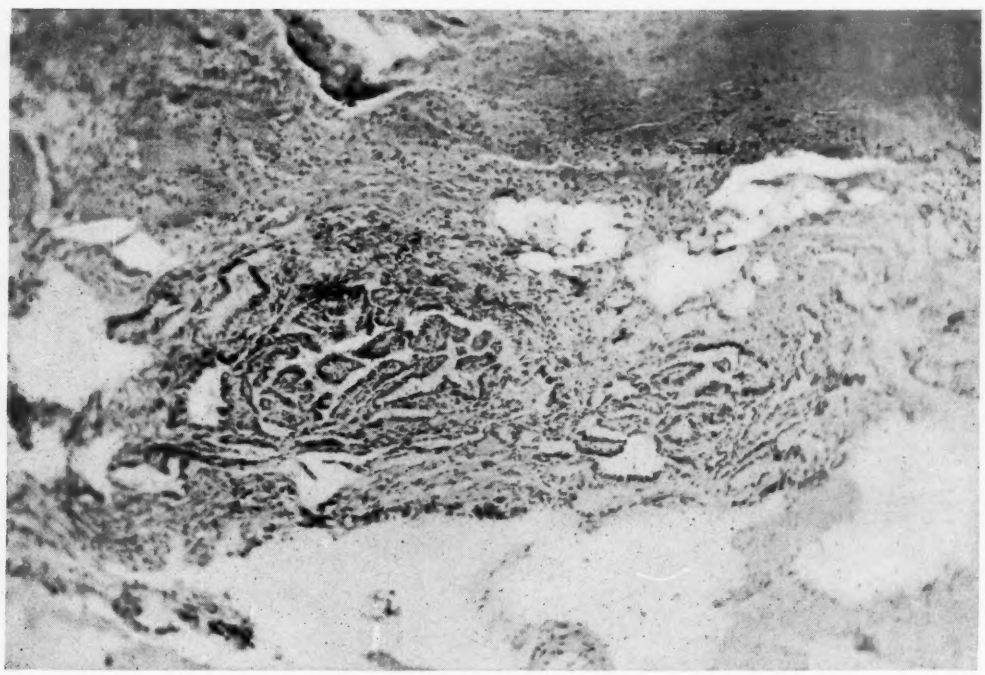


Fig. 2.—J. H. Biopsy No. 1 from left side. Tissue is fetal ovarian structure without follicles.



Figs. 3 and 4.—J. H. Biopsy from right side. Note mesonephric tubular structure and suggestion of ovarian cortical tissue.

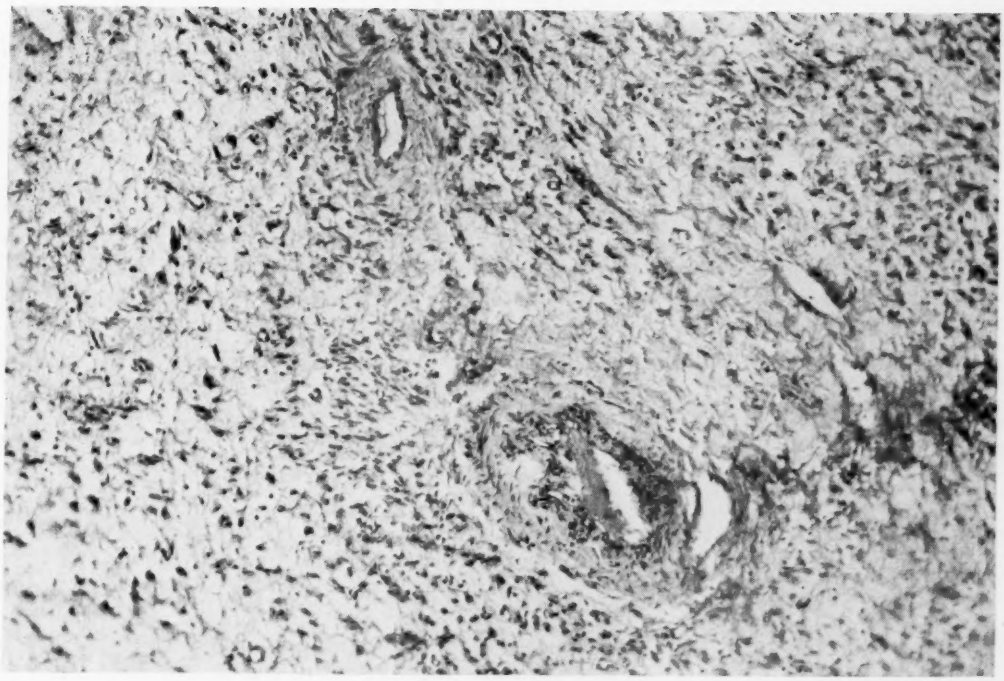


Fig. 4.—*(See legend for Figs. 3 and 4.)*

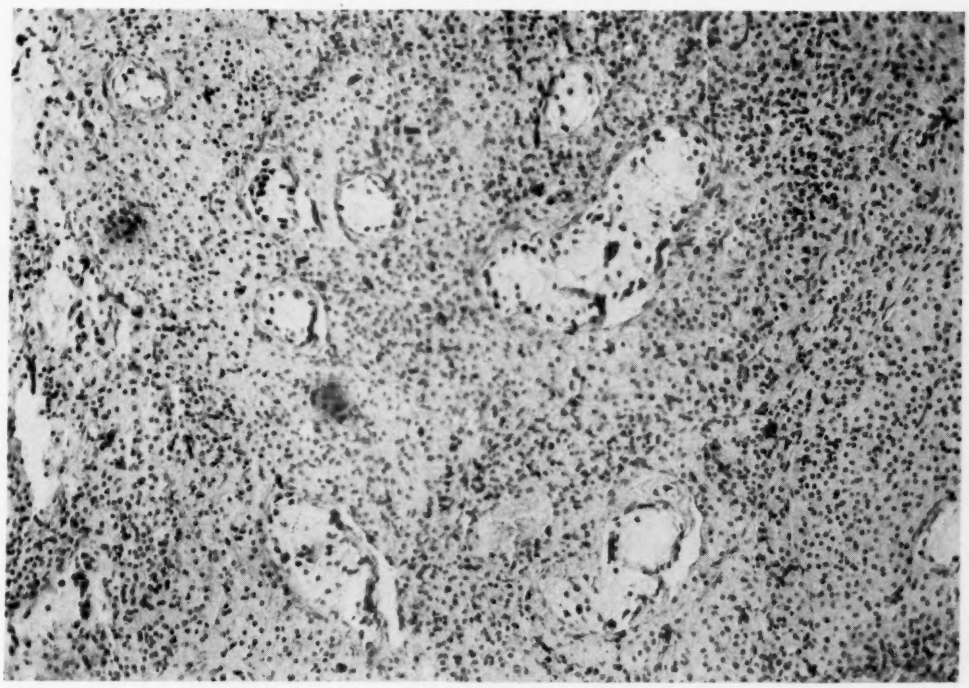


Fig. 5.—J. H. Biopsy from testis on right showing testicular tubules and interstitial tissue.

The patient's convalescence was again uncomplicated and *he* has since been discharged from the hospital. He acquired a man's name, haircut, and men's clothes. According to a recent letter from the patient, he adjusted well to the change, ". . . much better than I had ever dared dream." He has recently married, and writes that he is leading quite a normal life.

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731 Medical Arts Building

CONGENITAL ABSENCE OF ONE OVARY ASSOCIATED WITH CONTRALATERAL TUBAL PREGNANCY

JOSEPH A. KURCZ, M.D., AND MAHLON S. SHARP, M.D., LANSING, MICH.

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CONGENITAL absence of an ovary is an unusual finding, although White[1] in 1935 was able to collect seventeen cases in the world's literature, and about twenty-three cases have since been reported. An appreciable number of these cases have been in women who have borne one or more apparently normal children.[2, 3] One instance of tubal pregnancy associated with a deformed tube and aberrant ovary[4] was found, and another single instance of tubal pregnancy in a patient with only one tube and one ovary[5] has been described. Encountering these last-mentioned conditions which have apparently only once previously been reported makes the following case worth reviewing.

Case Report

Mrs. L. D., a 30-year-old white housewife, had been married about seven months when she was admitted to Woman's Hospital complaining of pain in lower abdomen and a feeling of weakness.

The present illness had begun fifteen days previously when, about two weeks after an expected menstrual period, she first noticed slight vaginal bleeding. She continued to feel well and performed her usual activities. After eight days of continued spotting, bleeding stopped for two days and then began more vigorously as a moderate bright red flow accompanied by irregular cramping pain in the lower abdomen. At bedtime the pain became more severe and she fainted. When she recovered, the pain seemed to be gone but returned two days later and this time was so severe that she remained in bed. She noticed small clots and the vaginal bleeding was slightly heavier than the usual menstrual flow. The abdominal pain became more severe and she called a doctor who sent her to the hospital by ambulance. Weakness was most marked at this time. The appetite had been poor for three days, although there had been no nausea, vomiting, or change in daily bowel habit. She had noticed no breast changes.

The past history revealed no operations or serious illnesses. The family history was not remarkable. She had been treated for cystitis in July, 1946, and cystoscopy was performed later.

The physical examination on admission revealed normal nutrition and feminine development. Skin and mucous membranes disclosed moderate pallor. The lips and tongue were dry. The heart, lungs, and breasts were not remarkable. The abdomen was moderately tender in the left lower quadrant. Vaginal examination was significant in that the posteriorly directed, nulliparous cervix was exquisitely tender on slight movement. The uterus was forward and nongravid in size and consistency. It was slightly fixed to an ill-defined tender mass in the left adnexal region.

The laboratory reported the urine to be normal except for numerous yeast cells. Hemoglobin was 12.6 Gm. per 100 c.c. of blood; R.B.C., 3,750,000; W.B.C., 9,000 per cubic millimeter of blood, with P.M.N., 86 per cent (F., 76 per cent; N.F., 10 per cent); basophiles, 1 per cent; and lymphocytes, 13 per cent. The department of radiology reported upon a retrograde pyelogram (Nov. 4, 1946) as follows: "Chronic pyelitis, bilateral, and beginning hydronephrosis on the right. No stones were visualized."

The patient was operated upon the evening of admission with the diagnosis of ruptured left tubal pregnancy. The abdomen was opened through a paramedian incision and about 200 c.c. of partially clotted blood was found in the lower peritoneal cavity. The uterus was small and in anterior position. The outer third of the left tube was distended and rup-

tured by a mass of clot and granular-appearing tissue measuring about 5 cm. in diameter and partially extruded through the defect in the wall of the tube. The area was markedly congested and slight hemorrhage was continuing. Before it could be removed, the mass and tube had to be freed from their adherence to the posterior surface of the broad ligament and the posterior surface of the uterus. The uninvolved portion of the left tube was of smaller than average diameter. The left ovary was larger than average and contained a prominent corpus luteum. The mesovarium was pedicle-like with a thick infundibulopelvic ligament with no discernible ovarian ligament. The ovary could be lifted freely out of the pelvis without tension on its lateral attachment. The round ligaments were of normal size and relationship to uterus and abdominal wall. The uterine cornua were equal and the uterus symmetrical although it deviated slightly to the right. The right tube was appreciably smaller than the left in the isthmic portion and continued as a barely palpable cord in the mesosalpinx which became an imperceptible fold of the broad ligament. The right ovary was not evident, either associated with the broad ligament or in the pelvis. The iliac fossa and cecal regions were searched and possible heterotopy excluded. Fecaliths were palpable in the lumen of the appendix which was then removed. Both kidneys were palpated and, with the gall bladder, were not remarkable.

The postoperative course was uneventful. The patient was ambulatory on the fourth day and discharged from the hospital on the eighth day.

The pathologist reported (1) ruptured ectopic tubal pregnancy; (2) inactive appendix. To this was added the following clinical diagnosis: congenital absence of the right ovary and hypoplasia of the right Fallopian tube.

Discussion

As in any congenital defect, a review of the embryologic development of the involved structures is illuminating.

The mesonephric body appears early in the human embryo (2.4 mm. length) and is fully developed with its duct opening into the cloaca by the end of the second month. Near the cephalic end of the mesonephros (wolffian body) an evagination of the lining of the body cavity into the genital ridge occurs. This evagination forms a tube, the müllerian duct. The converging lower portions of the müllerian and mesonephric ducts are embedded within a median band, the genital cord. The development of the ovaries begins about the time the müllerian ducts are forming. The ovaries are evident first as linear thickenings of the mesothelium and underlying mesodermal stroma on the median surfaces of the mesonephric bodies. The latter are enclosed and attached to the posterior body wall by mesenteries which continue as folds to the diaphragm and then inferiorly to the inguinal region. The early ovary is also provided with a mesentery that is continuous above and below with the folds of the mesonephros. The more important and prominent of the two is the lower plica in which lies a fibromuscular strand (the ovarian ligament) which below is attached to the müllerian duct. A second band of muscular tissue appears within the lower part of the inguinomesonephric fold and has as its upper attachment also the müllerian duct at a point about where it received the insertion of the ovarian ligament. The lower end of this band blends with the subperitoneal tissue in the vicinity of the future abdominal inguinal ring and later becomes the round ligament of the uterus. The müllerian ducts below the attachments of the ovarian ligaments fuse to form the uterus and vagina. Above the attachments they become the uterine tubes. The broad ligaments are formed by the enlargement of the primary peritoneal fold containing the müllerian and mesonephric ducts.[6]

Examination of the adult specimen does not tell us where in this orderly and integrated process interruption occurred, except that it was probably early. We may summarize then that in this case in the inguinomesonephric plicas the lower fibromuscular bands were normal, for both round ligaments were fully developed. The upper paired bands or ovarian ligaments originating on the ovaries and inserting on the müllerian ducts were of less than normal development on the left and indiscernible on the right, as was any significant development of the right ovary. Above the attachment of the round ligament on the right, the müllerian

duct was similarly and cephalad progressively involved in agenesia. This defect also, it is felt, was to some extent bilateral for at least some degree of hypoplasia of the left tube is believed to have been present.

In the case described the defect was less extensive than that in many previously reported, although in the five patients seen at Mayo Clinic[3] four of them had borne normal children. Lajos[7] reports Kossmann's analysis of twenty-two cases which revealed grossly normal uteri in six, and Reifferscheid, who with others, has observed that anomalies of the kidney are commonly associated with this defect and that the kidney and ureter of the same side may be absent. The kidney and ureter in this case were studied and showed no congenital defect. The ovary is more frequently absent on the right. Only five cases were encountered wherein this degree of agenesia was bilateral.

Curtis,[8] in discussing the etiology of tubal pregnancy, says that in the past, noninflammatory mechanical factors have been given too little emphasis and feels that congenital malformations may frequently be responsible for ectopic nidation. TeLinde[9] and others mention the not infrequent but difficult demonstrable diverticuli as occasional cause of gestation within the uterine tube. Other authors describe accessory ostia and lumina, excessive folding of the tubal mucosa, and the persistent fetal type tube which is long and much convoluted as possibly significant predisposing congenital conditions. It is also reasonable that simple hypoplasia with perhaps a much narrowed lumen and impaired peristalsis could be an explanation in this case.

Summary

1. A rare anomaly of unilateral absence of the ovary and partial agenesia of the corresponding tube has been described.

2. Ectopic pregnancy of the opposite tube occurred associated with this abnormality; hypoplasia of the tube is considered the probable etiology.

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312 Olds Tower Building

PREGNANCY FOLLOWING AN INTERILIO-ABDOMINAL AMPUTATION

(Sacroiliac Disarticulation or Hemipelvectomy)

HOWARD L. WILCOX, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

ONLY one other case of pregnancy following amputation through the sacroiliac joint has been noted in the literature. That case is reported by Judin,[1] a Russian surgeon. He did a radical amputation because his patient had a chondrosarcoma involving the upper third of the right thigh and the right inguinal region. Approximately five months after the operation she became pregnant. At term, the patient was admitted prior to the onset of labor so that a cesarean section could be done if necessary. However, she spontaneously delivered a 4,200 gram infant after one-half hour of labor. (That was her ninth baby.) When the patient was heard from one year after delivery, she was in good condition and had just stopped nursing her baby.

According to Pack and Ehrlich,[2] only one hundred thirty-two cases of amputation through the sacroiliac joint have been reported in the literature in the past fifty years. Six more cases were reported by Pack and Ehrlich. Thus, there is now a total of one hundred thirty-eight such cases. The case now being reported was presented, prior to pregnancy, in the hemipelvectomy series by Dr. Pack[2] (Case 4).

Case Report

The patient was a 24-year-old white primigravida. She presented herself in our obstetric clinic with a letter from the Memorial Hospital where the hemipelvectomy had been done. This revealed that on June 15, 1945, a left sacroiliac disarticulation had been carried out for a malignant neurofibroma of the von Recklinghausen type. It had involved the sciatic nerve and its branches and extended into the muscles of the thigh and buttock. The obturator foramen had been perforated and the pelvic parietes likewise were involved. One year after her operation the patient married. Her last menstrual period was on Aug. 2, 1946. Her expected date of confinement was computed to be May 9, 1947. When the patient was first seen in the obstetric clinic, the general physical examination was essentially unremarkable except for the sacroiliac amputation. Her serology was negative and she was found to be Rh negative. Repeated transfusions had been given to the patient during and following the operation. On closer examination of the operative site, some tenderness was noted and the labia on the left were edematous. Rectal examination revealed a mass extrinsic to the bowel which caused a partial occlusion of the rectum. In January of 1947 it was apparent that this mass was enlarging. Therefore, the patient had an aspiration biopsy done at the Memorial Hospital which revealed a neurosarcoma, considered to be recurrent in origin. After careful evaluation, it was felt that the prognosis of the patient was hopeless, and therefore the pregnancy should be allowed to continue, with the hope of getting a live baby. Pain throughout the surgical stump, lower abdomen, and back became quite constant and annoying. Sedatives and analgesics were administered, and it was planned to give palliative x-ray therapy after delivery of the infant.

On March 11, 1947, the patient was admitted to the obstetric service with the signs of early premature labor. The pain in the stump had become excruciating in nature. There was some bowel distention associated with nausea and vomiting. This was controlled with supportive measures. The uterine contractions were stopped with the use of morphine. Two days later, vaginal examination revealed the presence of marked edema of the left

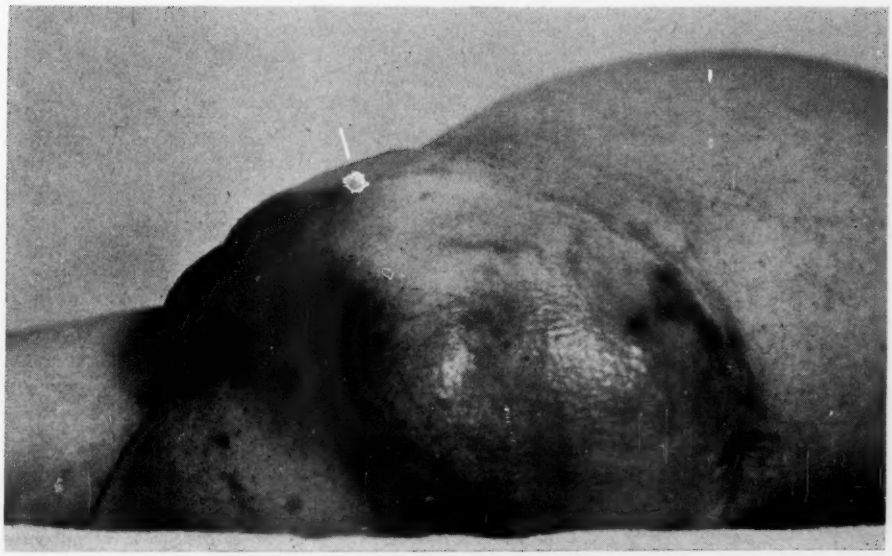

Fig. 1.—Lateral view of patient revealing surgical absence of the left leg. The left side of the pelvis (the bony wall of which was removed) is now replaced by tumor mass. Note edema and discoloration of the overlying skin and the marked edema of the left labia.

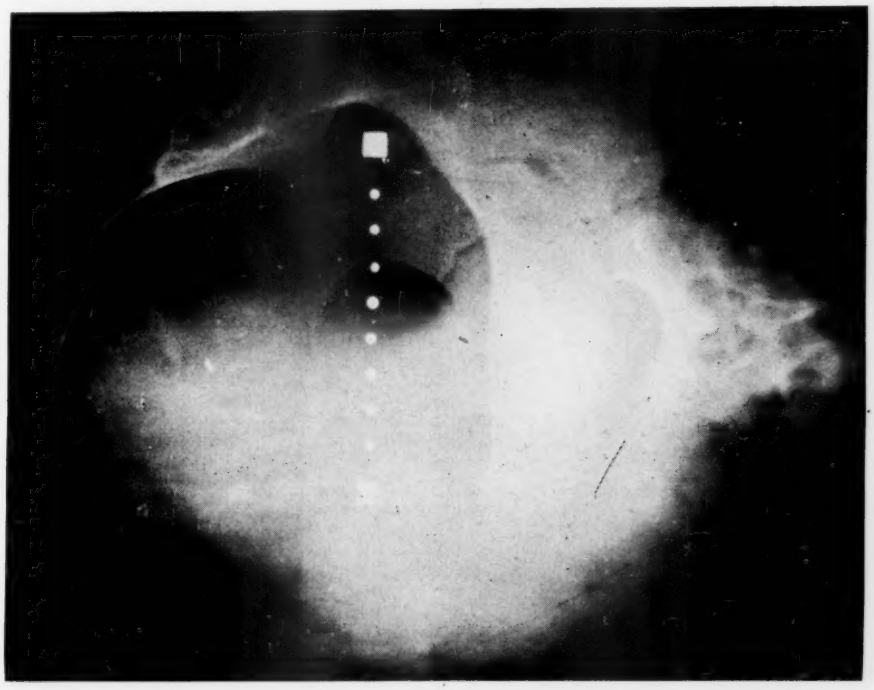

Fig. 2.—X-ray of the pelvis reveals absence of the bony structures on the left. Note soft tissue mass on left side extending over to the midline of the pelvis.

labia. There was some relaxation of the vaginal canal. The obstetric conjugate was ample. On the left side, a hard spherical mass extended to the midline. X-rays of this area revealed a large, soft tissue mass that extended to the sacrum with evidence of bony erosion.

The clinical course was rapidly downhill. Anorexia, nausea, and vomiting developed. Intravenous fluids, transfusions, and sedatives were administered. A low-grade temperature developed. It was apparent that the patient would not live to go to term. The fetus was estimated to be about 2,200 to 2,300 grams. Since the patient was Rh negative, her blood was tested for antibodies; she was found to have a weak blocking antibody titer of 1:2 and 1:4. On March 20, a classical cesarean section was carried out in an attempt to get a living baby prior to the certain exitus of the patient. A 2,500 gram male infant was born and appeared to be in good condition. A specimen of cord blood revealed the infant to be Rh negative. Unfortunately, the baby did not do well during the next few days. Marked edema and jaundice developed and, fifty-eight hours after delivery, the infant expired. Autopsy examination revealed the baby to have atelectasis with marked edema and jaundice.

The mother was given supportive measures following the cesarean section. This consisted of multiple transfusions of whole blood, infusions of plasma, glucose, and vitamins. Progressive weakness, edema, pleural effusion and pneumonia developed. On April 11, 1947, the patient expired.

The significant autopsy findings revealed the presence of multiple neurogenic fibromata with neurogenic sarcoma of the left buttock. The left femoral and sciatic nerves, together with most other nerves distal to the intervertebral foramina in this region, were irregularly and several times enlarged by firm gray-white tumor tissue. Densely adherent to these nerves, extending laterally into the left buttock and medially invading the sacrum was a 20 by 15 by 15 cm. firm gray-white mass with small central areas of hemorrhage and necrosis. Many nerves throughout the body, including both vagi, phrenics, and the right femoral and sciatic nerves, were greatly (up to about eight times normal size), but variably, often locally, enlarged. Metastatic sarcoma was noted by the invasion medially into the sacrum. There was also a single (1 by 0.5 cm.), gray-yellow, firm metastatic tumor nodule beneath the pleura of the upper lobe of the left lung. Together the lungs weighed 1,300 grams and were markedly hyperemic and edematous with large firm areas of consolidation in all lobes. There was a firm red infarct, measuring 4 cm. across, in the lower lobe of the left lung, with a medium-sized artery occluded by a firm grayish red thrombus. Staphylococcus aureus hemolyticus and a pneumococcus, unclassified, were grown from the lungs post mortem.

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Correspondence

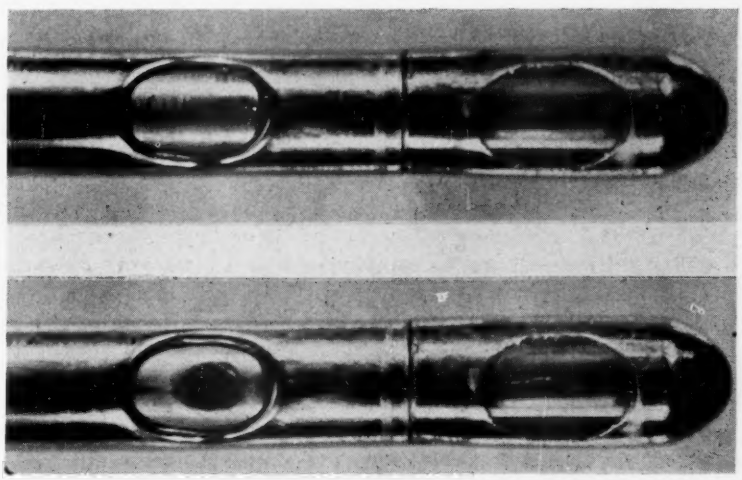
Culdoscopy

To the Editor:

I have read with great interest the article on culdoscopy published by R. W. TeLinde and F. Rutledge in the January, 1948, issue of the JOURNAL. As far back as 1936, I introduced the first instrument designed for this type of examination and named it colpolaparoscope. Having gained considerable experience with colpolaparoscopy (method of entering the abdominal cavity through the fornix vaginae), I wish to state that I am in complete agreement with the aforementioned authors, that colpolaparoscopy (c. 1.) is a useful adjunct to the diagnostic armamentarium in gynecology. However, it should be stressed that, in addition to colpolaparocentesis as a therapeutic measure in conditions associated with ascites, I used the operative colpolaparoscope for minor surgical procedures such as the dissection of adnexial adhesions, fimbriolysis, and the securing of biopsies.

My instrument was manufactured in Vienna, in 1936, by the Leiter Company. It is equipped with an elaborate optical system, and a device which prevents the lenses from becoming soiled within the abdominal cavity. The lenses are covered during the introduction of the instrument. (Fig. 1*A*.) With the instrument in situ, the rod equipped with the optical system is rotated within its sheath clockwise 180 degrees. Thus the lenses are set free. (Fig. 1*B*.) Two close-up pictures of the proximal part of the instrument, demonstrating this mechanism, are attached; also a picture of all the component parts of the instrument (Fig. 2).

A.



B.

Fig. 1.

Only when the examiner is certain that the cul-de-sac of Douglas is free should the brusque penetration in knee-chest position be attempted. In all other cases, the anatomic approach to the pelvic cavity through a 1 cm. wide incision in the posterior fornix, with exposure of the rectovaginal space and the peritoneal reflection, is preferable. This approach was advocated by me in presentations before the Viennese Medical Society, 1937, and the New York Academy of Medicine, 1947, and described in Wien. klin. Wchnschr. **59**: 50, 1947. The delay in publication was due to the war and postwar conditions. By the ana-

tomic approach to the cavity of Douglas, its contents, such as blood or exudate, will not escape the attention of the examiner, and injuries to a viscus and extra- or retroperitoneal emphysema will be avoided. Failures to penetrate into the abdomen, as encountered by Rock in one out of every six of his cases, may thereby be markedly reduced.

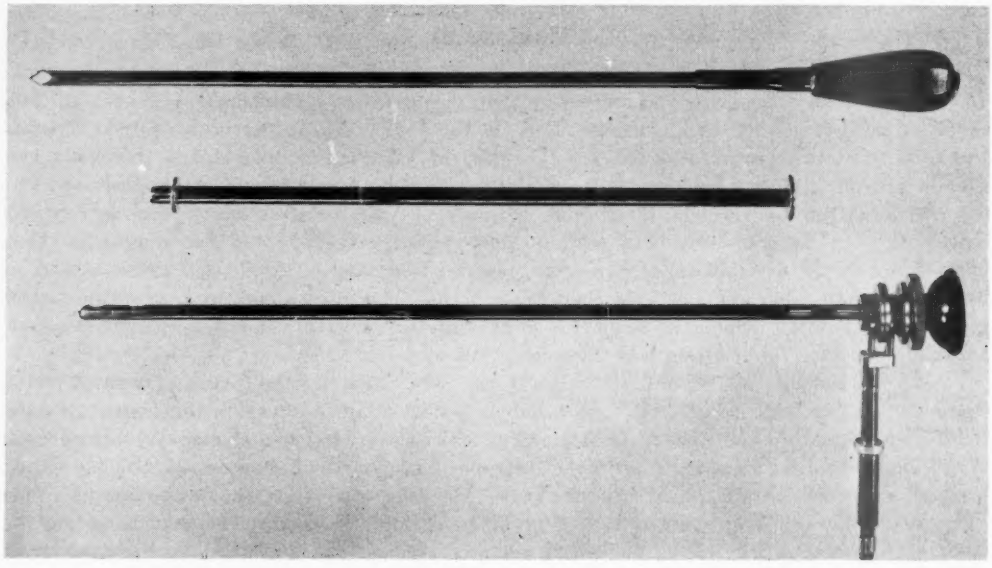


Fig. 2.

We have used two methods of introduction of the instrument: (1) in Trendelenburg position with the operating table tilted at an angle of 45°, with air insufflation and an intrauterine probe, which keeps the uterus in position; (2) in knee-chest position. In either case the instrument should be inserted with its promixal end directed toward the center of an imaginary line, which connects the promontory with the umbilicus.

There are two definite and strong indications for performing a colpolaparoscopy: (1) all instances suggestive of ectopic pregnancy (peritubal hematoma, hematomole, early tubal abortion, etc.) where otherwise, a diagnosis cannot be made with certainty; (2) cases of ovarian or tubal carcinoma or cancers of adjacent pelvic organs. In these two categories, a definite diagnosis can be established and a lifesaving operation performed without delay. Episodes, such as torsion of the uterus or adnexa or bleeding from a ruptured corpus luteum, can be diagnosed and treated surgically. Furthermore, it is helpful in avoiding unnecessary laparotomies in cases of subacute and chronic inflammations, in small fibroids, which by virtue of their localization are often mistaken for ovarian tumors, in endometriosis, etc. There is also a definite place for examination in cases of sterility due to ovarian conditions, such as infantilism or adnexial adhesions, both of which can easily be visualized, and the latter sometimes successfully treated with the operative colpolaparoscope. However, in order to guard the new method against becoming discredited, it should never be performed indiscriminately. The method is definitely contraindicated in febrile conditions or infectious diseases of the genital tract and its adjacent organs.

The valuable contributions by TeLinde and Rock will hasten the introduction of the procedure into gynecology. May I add that the foregoing communication is not intended to detract from the valuable work of Dr. Decker.

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NEW YORK
Feb. 14, 1948

Cesarean Section Scar

To the Editor:

I have been much interested in the study of cases of rupture of the abdominal scar of previous cesarean sections, from the Boston Lying-in Hospital, as presented by Daniel H. Hindman, in the February number of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

While I was a member of the Staff of the Maternity Hospital of Cleveland, we saw a patient who had had a previous section because of disproportion. We brought this patient into the ward for the last few weeks of her next pregnancy. At the first intimation of labor, a repeat section was started. On opening the abdomen, I found the line of the former classic section in the uterine wall was represented by a soft red stripe of granulation-like tissue. At one point, this had already separated for a distance of some two centimeters. Through this opening, the unruptured fetal membranes herniated. The gloved finger introduced here easily separated the entire length of the old incision, and the baby was delivered without the use of any incision in the uterine wall. Microscopic examination of the red tissue forming the old scar showed it to be endometriosis extending from the uterine cavity. In weighing the pros and cons for a repeat section, this possible weakening of the old scar should be borne in mind.

Another factor that should be studied, when the question of section or vaginal delivery must be decided in such cases, is the position of the placenta. I was impressed—I think there were four cases—with the apparent fact that a placenta on the front wall of the uterus makes the old scar of a classic section more vulnerable. Possibly this is due to invasion of trophoblast and increased vascularity under the placenta. By noting the direction of the round ligaments, or by x-ray, it is usually possible to tell whether the placenta is on the anterior or the posterior uterine wall. That position is well worth evaluating in making a decision about the need for repeat section.

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BOSTON, MASS.
MARCH 24, 1948.

Erratum

In the article by Peter J. Talso and William J. Dieckmann, entitled "Anemias of Pregnancy," in the March issue of the JOURNAL, the accompanying two illustrations were printed with the explanatory material deleted. They are reproduced here with their complete legends.

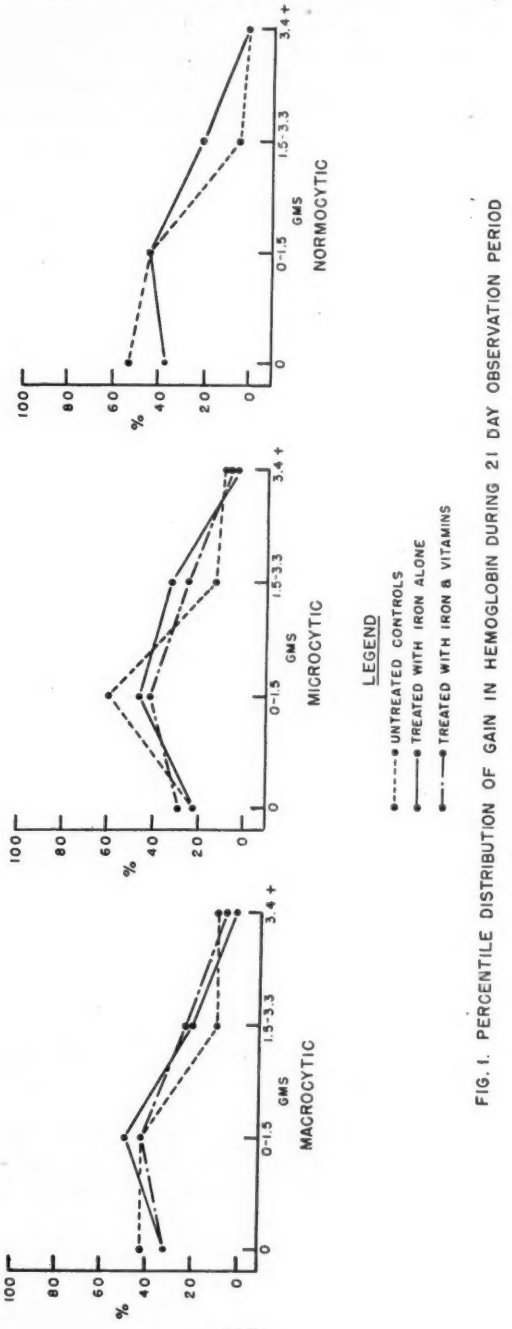

FIG. 1. PERCENTILE DISTRIBUTION OF GAIN IN HEMOGLOBIN DURING 21 DAY OBSERVATION PERIOD

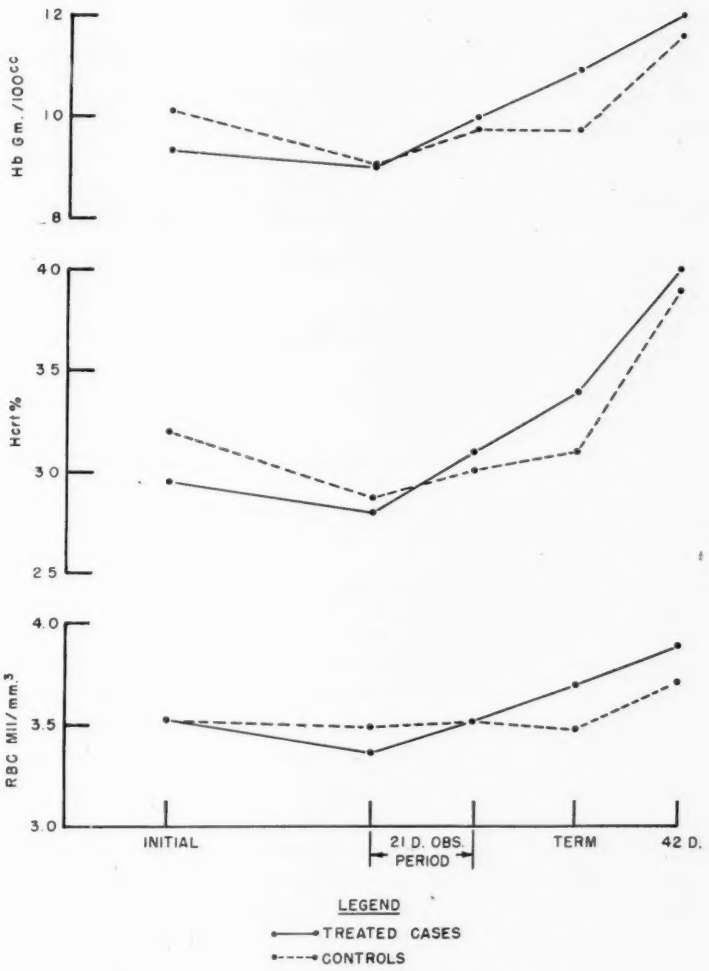

FIG. 2. MEAN VALUES FOR HEMOGLOBIN, HEMATOCRIT AND RED BLOOD CELL COUNT.

Erratum

In the article by Wesley Bourne, entitled "Wise Indifference of the Wise in Anesthesia," in the April issue of the JOURNAL, on page 714, in the nineteenth line, the word "either" should read "ether"; on page 715, in the thirty-seventh line, the word "pyruvid" should be "pyruvic."

Department of Reviews and Abstracts

Selected Abstracts

Menopause

Ingiulla, W.: Endocrine Factors and Abnormal Uterine Bleeding During Climacteric, Riv. Ital. di Ginec. **28**: 77, 1945.

Profuse uterine bleeding during the climacteric, without anatomic change in the womb, was observed in nineteen cases by Ingiulla in the Department of Gynecology of the Medical School in Florence. None of the patients in this group showed the more common climacteric signs of hyperactivity of the corticoadrenal system, such as flushes, hypertension, adiposity, or hirsutism. Signs and symptoms reminiscent of hyperthyroidism, however, were frequently present, such as tremor, instability, and insomnia.

The research work is based on painstaking observation of clinical signs and symptoms, and findings are interpreted according to the teaching of De Giovanni and Marañon.

Climacteric patients with essential bleeding observed by Ingiulla showed constitutional characteristics usually seen in the so-called underdeveloped or juvenile type.

According to Inguilla, juvenile constitution with latent hyperthyroidism seems therefore to be the foremost underlying factor in essential profuse bleeding during the climacteric.

GEMMA BARZILAI.

Cazzola, D., and Mosconi, G.: Saccharomyces in the Vaginal Cycle, Riv. Ital. di Ginec. 29: 152, 1946.

Cazzola and Mosconi of the Obstetrical and Botanical Department of the Medical School of Pavia made proportional countings of saccharomyces colonies, cultivated from the vagina of six healthy women. Saccharomyces appeared to be a normal finding in the vaginal content of healthy, normally menstruating women.

The proportional counting of the colonies also showed a definite pattern of rising and falling, according to and coinciding with the different periods of the monthly cycle. Highest values were found around the twentieth day of the cycle, with progressive rising from the tenth to the twentieth day of the cycle (intermenstrum). Lowest values were found during actual menstrual flowing with progressive fall starting after the twentieth day of the cycle.

Saccharomyces are found again in cultures made five to six days after cessation of the menstrual flow, and they rise progressively until the twentieth day.

During the monthly pregnancy, colonies of saccharomyces are extremely numerous.

During the monthly cycle, highest value of saccharomyces coincide with the period in which the vaginal epithelium is richest in glycogen and the chemical reaction is more definitely acid (pH about 4.5).

GEMMA BARZILAI.

Newborn

Bianchi, P.: Polycystic Ovaries in a Fetus, Riv. Ital. di Ginec. 28: 301, 1945.

P. Bianchi of the Medical School in Florence describes a case of bilateral polycystic ovary in a fetus in which follicles were developed to different stages as corresponding to findings in infancy and adolescence in which, however, maturing follicles had undergone regressive changes before reaching full maturity.

The ovary harbored primordal and primitive follicle and was studded with small cystic follicles, mainly lined by flat epithelium. The anterior lobe of the hypophysis showed in this case the histologic picture usually seen in a grown-up woman. Well-developed eosinophilic and basophilic cells were present, and interspersed with chromophobes. Basophiles were decidedly increased in number, and comprised 10 per cent of the cells which speaks in favor of the sexual function of basophilic cell activity. The thyroid gland also showed the features pertaining to adult life. The case presentation is completed by speculations as to the interrelationship of the maternal endocrine system to the endocrine system of the fetus. GEMMA BARZILAI.

Editorial: What Is Epidemic Diarrhea of the Newborn? New England J. Med. 236: 115, 1947.

The American Academy of Pediatrics describes epidemic diarrhea in the following manner: an infant in the neonatal period who, previously well, suddenly passes one or more very loose or liquid stools combined with sudden abnormal loss of weight (after the period of initial weight loss) or one of the other symptoms associated with this type of diarrhea, such as vomiting, listlessness, drowsiness, refusal of feeding, short feeble cry, pallor, or elevation of temperature, should be immediately isolated and reported to the hospital authorities as a suspected case of infectious diarrhea.

The lack of knowledge regarding the etiology of epidemic diarrhea of the newborn adds to the confusion that obscures diagnosis in the individual case.

A control program would consist of periodic inspections of all hospital nurseries by the Board of Health to ensure that institutions providing care for the newborn were operating according to standard procedures. Overcrowding of nurseries, insufficient personnel improper making of formulas and faulty sterilizing techniques emphasize the need for greater diligence on the part of those responsible for the care of newborn infants.

JAMES P. MARR.

Rubenstein, A. Daniel, and Foley, George E.: Epidemic Diarrhea of the Newborn in Massachusetts, New England J. Med. 236: 87, 1947.

It is the purpose of this discussion to review nineteen outbreaks of epidemic diarrhea of the newborn as reported to the Massachusetts Department of Public Health from 1935 to 1945. In the 258 cases reported, eighty-five patients died, giving a case mortality of 33 per cent.

The etiology and mode of transmission of epidemic diarrhea in the newborn nurseries where these outbreaks occurred revealed many inadequacies. Overcrowding, insufficient personnel, general use of a common rectal thermometer, and inadequate supervision of formula making were frequently encountered.

In several outbreaks, apparently identical organisms were isolated from sick and healthy infants, nursery personnel, and formulas. The presence of Group D, streptococci in the throats of infants with epidemic diarrhea of the newborn suggests that, as a result of poor nursery techniques, infants may be exposed to organisms that are normally found in the human intestinal tract. JAMES P. MARR.

Dodd, Katharine, and Papoport, S.: Intravenous Alimentation of Infants, J. Pediat. 29: 758, 1946.

This report deals with experience acquired during the past year and one-half with the administration to infants by venoclysis of all, or the majority of, the needed elements of nutrition for periods up to fifteen days. Most of the children suffered from chronic or recurrent diarrhea and vomiting. The aim was to supply adequate fluid and salts, and at least maintenance amounts of calories and proteins.

A daily record of the total intake of fluids, saline, calories, and nitrogen as part of a careful plan is an essential prerequisite of such a program.

With the use of glucose, whole blood, plasma, and casein hydrolysate, a gain in weight may be achieved. Premature and very young infants require less saline in proportion to their body weight than do older infants.

The author warns of the danger of infection at the site of infection of casein hydrolysate. Thrombophlebitis and wound infection continue to be troublesome.

JAMES P. MARR.

Knop, Catharine: The Dynamics of Newly Born Babies, J. Pediat. 29: 721, 1946.

The author has studied the muscular energy or "dynamics" of 689 infants, who were examined twice during their eight-day stay in the hospital.

No definite correlation could be established between babies' weights and their dynamics.

The relation of the mothers' labor or sedatives received or the method of delivery to the grading of dynamics was inconclusive.

The author is of the opinion that the dynamic reaction determined at different times and even by different examiners remained essentially unchanged, supports the impression that a persistently inherent quality underlies reactions during the neonatal period.

JAMES P. MARR.

Salmon, George W., Forbes, Gilbert B., and Davenport, Harbert: Airblock in the Newborn Infant, J. Pediat. 30: 260, 1947.

The authors define airblock as that condition produced by escape of air from the normal respiratory pathways into tissues in which it is not normally present.

Since some of the terms used are long and awkward, they have substituted the abbreviation PIE for pulmonary interstitial emphysema, ME for mediastinal emphysema, and PT for pneumothorax.

The most reliable way of demonstrating PIE at autopsy is to enter the pleural spaces under water. Six cases are reported. Macklin was of opinion that the most likely and probably the most common sequence of events is as follows; air first passes through multiple and minute ruptures of the alveolar walls which border upon blood vessels, to form perivascular collections of air. From here air progresses along the blood vessels to reach the mediastinum. From the mediastinum the air may travel superiorly to produce cervical subcutaneous emphysema, or travel inferiorly to produce retroperitoneal emphysema and pneumoperitoneum. Also, from the mediastinum the air may travel into the interstitial tissue of the other lung, rupture into the pericardial sac, or rupture the mediastinal pleura to enter the pleural sac.

All patients showed evidence of anoxia. Amniotic fluid was stained with meconium in three cases. Two patients had intracranial hemorrhages, while one had a blood cisternal fluid but no autopsy of the head.

As treatment, the authors state that if the symptoms are mild, spontaneous recovery will likely ensure by increasing the oxygen concentration of inspired air.

If a large PT is present, aspiration is advisable. If a tension PT recurs a closed thoracotomy is performed and connected to a water trap so as to allow air to escape but not enter.

JAMES P. MARR.

Pregnancy

Ingerslev, Magens, and Teilum, Gunnar: Biopsy Studies on the Liver in Pregnancy. II. Liver Biopsy on Normal Pregnant Women, Acta obst. et gynec. Scandinav. **25:** 352-360, 1945.

The authors, working at the Lying-In Department of Rigshospital, Copenhagen, used Iversen and Roholm's technique for biopsy of the liver (performed by the latter on more than 1,000 cases) to obtain liver aspiration biopsies on 17 normal pregnant women. The purpose of their study was to re-evaluate the so-called "pregnancy liver" by histologic studies on such specimens.

Ingerslev and Teilum observe that the massive histologic changes in the liver reported by Hofbauer, in 1908, during normal pregnancy could not be confirmed by either post mortem or aspiration biopsy histologic studies. Accordingly, they conclude that the connotation "pregnancy liver" cannot be maintained as an histological concept.

The writers close their article with the observation that while several physiological and biochemical findings indicate that pregnancy is associated with certain changes to the intermediate metabolism localized to the liver, there are no pathophysiological reasons to maintain the concept of the "liver of pregnancy." One chart and two photomicrographs accompany the article. C. E. FOLSOME.

Ingerslev, Magens, and Teilum, Gunnar: Biopsy Studies on the Liver in Pregnancy. III. Liver Biopsy in Albuminuria of Pregnancy, Eclampsism and Eclampsia, Acta obst. et gynec. Scandinav. **25:** 361-376, 1945.

In this concluding paper of a triad of articles preceded by two others concerned with biopsy studies of the liver in normal nonpregnant and pregnant women, the authors focus their attention upon utilization of these same methods for the histopathologic study of the liver in three types of toxemias, pre-eclampsia and eclampsia.

In their series of eight cases of albuminuria of pregnancy, and in six cases of pre-eclampsia, neither the clinical examination nor histologic examination of the liver, removed in biopsy, revealed any definite signs of a liver lesion. The histologic studies observed in these conditions were quite in keeping with that obtained in the control material for the normal nonpregnant and the normal pregnant woman's specimens.

Among the five cases of eclampsia two patients showed a perfectly normal histologic picture, while one presented some slight degenerative changes, and two showed characteristic peripheral precipitation of fibrin with necrons and hemorrhage in an otherwise perfectly normal liver tissue. Thus pronounced histologic changes have been demonstrated only in patients with fully-developed eclampsia. Even severe histopathologic changes are found not to be incompatible with patient survival.

The writers conclude that the fibrinous precipitates were taken to constitute the essential feature in the pathologic picture—and perhaps also the central factor in the production of the convulsive seizures. There are three tables and five photomicrographs accompanying the article. C. E. FOLSOME.

De Giorgi, Luigi: About So-Called Chorionic Infiltration, Arch. di ostet. e ginec. **51:** 207, 1946.

De Giorgi reviews the material of the University of Naples related to abnormalities of placentation. Microphotos of accrete placenta, vesicular mole, infiltrative mole, and chorion-epithelioma are presented. Data related to differential diagnosis of these entities are discussed. The existence of chorionic infiltration as a peculiar entity, different from the above-named hyperplastic and neoplastic aspects of placentation, as formerly advanced by Poso and Miranda, is denied by De Giorgi on the basis of the material he had the opportunity to study.
GEMMA BARZILAI.

Lewis, J. M., Bodansky, O., Lillienfeld, M. C. C., and Schneider, H.: Supplements of Vitamin A and of Carotene During Pregnancy, Their Effect on the Levels of Vitamin A and Carotene in the Blood of Mother and of Newborn Infant, Am. J. Dis. Child. **73:** 143, 1947.

Seventy-four women were given 10,000 units of vitamin A or of carotene during the last few months of pregnancy in order to determine whether these supplements would prevent the fall of vitamin A in the blood which normally takes place in the last trimester.

Dark adaptation tests are now being carried out on a large group of pregnant women to ascertain whether the low levels of Vitamin A are associated with poor dark adaptation which, as had been shown in previous studies on infants and children, becomes detectable when vitamin A deficiency is of moderate or profound degree. The authors noted that at present there is no evidence that low concentrations of vitamin A in the blood of pregnant women are associated with clinical manifestations of vitamin A deficiency.

The result of this study indicates where vitamin A, which is supplemented in the aforementioned dosage, brought about a maintenance of good levels of vitamin A during the last phase of pregnancy. JAMES P. MARR.

Fouracre-Barns, H. H.: Retrodisplaced Gravid Uterus, Brit. M. J. 4491: 169-172, 1947.

The author reviews 66 cases with a retrodisplaced gravid uterus. He makes a plea for conservative treatment of the sterile woman with a retroversion and suggests that operative correction of a retrodisplaced uterus for a previous abortion is unwarranted.

In the writer's experience incarceration occurs between the thirteenth and seventeenth weeks of pregnancy, and he discusses two cases of sacculation of the incarcerated gravid uterus. The cardinal symptoms of incarceration was sudden onset of urine retention with lower abdominal pain. His conservative treatment includes gradual bladder decompression, watch-spring pessary, urinary antiseptics—with emphasis upon posture and pessary for those not incarcerated. C. E. FOLSOME.

Aviles, V., Manuel: Our Experience With Cardiac Patients During Pregnancy, Obstet. y Ginec., Latino-Am. **4:** 571-584, 1946.

In the author's maternity hospital there were 472 cases of cardiac disease among 52,485 pregnant women during the last ten years. This is an incidence of 9 per cent. There were forty-nine instances of heart failure and among these women five died. In spite of the many cases of cardiac failure which occurred during pregnancy, the total mortality for the women with valvular disease was only 2.91 per cent. The author emphasizes that the capacity of the muscle is not the only important consideration in the care of patients with heart disease. The occurrence of failure can be avoided by instituting treatment early. This consists of proper diet, rest and intermittent digitalization. Therapeutic abortion is rarely indicated in cases of heart disease and it should be reserved for patients with serious and repeated accidents such as total arythmia and auricular fibrillation. There were only five abortions in this series. J. P. GREENHILL.

Garcia Huidobro, M., and Paredes, L.: The Friedman Reaction in the Cerebrospinal Fluid and Its Importance in the Diagnosis of Hydatid Mole, Bol. Soc. chilena de obst. y ginec. **11:** 31-34, 1946.

The authors report a series of 13 Friedman tests performed on the cerebrospinal fluid. Of four women with hydatid mole the test was positive in three and negative in one. The authors attribute the negative result to the small amount (5 c.c.) of spinal fluid used for the test. In three cases, Friedman tests on the spinal fluid were performed two, ten, and forty-eight hours, respectively, after expulsion of the mole, and in all three the tests were positive. However, in two women tests were carried out on the fourth and seventh days respectively

after expulsion of the mole and the tests were negative. Tests were performed in four control women without hydatid mole and all the tests were negative. From their study the authors conclude that Friedman tests performed on 10 c.c. of spinal fluid are of great assistance in the diagnosis of hydatid mole. J. P. GREENHILL.

Cabrera, S. H.: Some Considerations of Hydatid Mole, Bol. Soc. chilena de obst. y ginec. **11:** 39-55, 1946.

At the San Borja Maternity, among 77,947 pregnancy cases, there were 15,142 abortions and 94 hydatid moles. The hydatid moles were discovered in pregnancy as follows: one month, 1; two months, 22; three months, 36; four months, 23; five months, 6; six months, 3; and seven months, one. Most of the moles were expelled spontaneously at the third and fourth months, and the majority were not expelled completely. Hemorrhage was usually severe enough to require blood transfusion. The total mortality was 0.94 per cent.

The authors emphasize that as soon as the diagnosis is made, the uterus should be emptied. In not a single case of the authors has a chorionepithelioma developed. This has been proven both by repeated clinical examinations and by biologic gonadotropin tests.

J. P. GREENHILL.

Toxemia

Parviainen, Sakari: An Investigation of the Manifestation of Precursory Symptoms of Nephrogestosis and Their Importance for the Prognosis of Parturition, Ann. Chirurg. et Gynec. Fenniae **35:** Supplement 1, 1946.

The author presents an analysis of the 5,557 women who received antenatal care at the Maternity Center in Helsinki in the years 1942 and 1943. Of this number, 1,418 showed symptoms of nephrogestosis or signs of a potential outbreak of the disease. The diagnosis of this condition was based on the finding of any or all of the following: albumin in the urine, elevated blood pressure, and edema. Attention is called to the fact that edema is the first finding which suggests nephrogestosis; high blood pressure usually makes its appearance shortly thereafter, and it is not until much later that albumin appears in the urine. Of the 1,418 cases, sixty-six were classified as pre-eclampsia, and eight actually developed eclamptic convulsions. The author admits that his statistical analysis is somewhat confused because of the difficulties imposed as a result of the war. However, it is interesting to note that there was a significant fall in the number of cases of nephrogestosis and, to a lesser extent, in the number of cases of actual eclampsia during the war years.

It is suggested that, even though apparently unnecessary work will be involved, if we are to reduce substantially the number of cases of nephrogestosis occurring in parturition, the patient must be seen more frequently prenatally, and careful check made for the presence of elevated blood pressure, edema, and albuminuria. HERBERT J. SIMON.

Schneider, Charles L.: The Active Principle of Placental Toxin: Thromboplastin; Its Inactivator in Blood: Antithromboplastin, Am. J. Physiol. **149:** 127-129, 1947.

Schneider believes he has demonstrated that the toxin from tissue extracts, especially placental extracts, possessing such toxin, long suspected as a causative agent in the toxemia of pregnancy, is thromboplastin and that its lethal effect depends on intravascular clotting. The author lists six reasons he believes support the possibilities that thromboplastin is actually the causative agent in toxemia of pregnancy. (1) The anatomic lesions of eclampsia are consistent with the underlying lesion being multiple thrombosis. (2) The concentration of antithromboplastin of the blood increases during pregnancy. (3) Anatomic relationship does not preclude that thromboplastin from the placenta can enter the maternal blood stream. (4) Pregnant animals are more sensitive to thromboplastin than are non-pregnant animals. (5) In the few recorded moribund toxemia patients the blood clotting time is prolonged else the

blood fails to clot and fibrinogen is often decreased in concentration or is even absent. (6) There are two literature reports that the "neutralizer" in serum (therefore antithromboplastin) is markedly decreased in eclamptic patients.

Schneider concludes that antithromboplastin is the inactivator of the toxin, thromboplastin and while actual proof is lacking there is no evidence to the contrary that thromboplastin might be the cause of toxemia of pregnancy. C. E. FOLSOME.

Fertility, Sterility

Murless, Bryan C.: A Review of the Present Position of the Investigation of Sterility and Infertility in the Female, South African M. J. 20: 788-793, 1946.

The author reviews, in superb English and in a singularly well-organized manner, the methods of investigation of female sterility. He re-evaluates the older approaches to this problem but adds much new data, presently available only in scattered texts and recent articles, in such a fashion as to clearly summarize the knowledge on this phase of gynecology up to 1946.

He concludes that the investigation of sterility is essentially negative in character, as the factors which determine fertility in the female are so varied. His cardinal object is to eliminate the known causes of infertility. Murless agrees that actual proof of fertility is not obtainable until conception has taken place. C. E. FOLSOME.

Rommer, J. Jay: Psychoneurogenic Causes of Sterility and Their Treatment, With Preliminary Remarks on Allergenic Sterility, West. J. Surg. 55: 278, 1947.

To the ancient Greeks and Romans and to the others of lesser historical statue, the author turns to observe the incantations and religious practices designed to alleviate the sterile state. He considers the psyche in relation to sterility under two broad classifications: psychogenic sterility and neurogenic sterility.

Mental disorders, fears or anxieties, depressions and psychic trauma, sexual perversions and frigidity may disturb the normal pituitary ovarian endometrial cycle. A heavy outpouring of adrenalin, associated with some of these psychic states, may produce castration-like changes in the anterior pituitary.

The Rubin kymograph was set up with a 15 c.c. balloon in the vagina to record vaginal contractions during a manually induced orgasm. It was observed that the vaginal muscles become more contractile, while the uterus remains quiescent. Allergy and associated conditions may cause sterility by inducing an edema in the cervix and endometrium.

WILLIAM BICKERS.

Brooks, Matilda Moldenhauer, The Mechanism of Fertilization of Eggs, Growth 10: 391-410, 1946.

Brooks, using the eggs and sperm of *Arbacia, Asterias* and *Chaetopterus,* began her studies upon the hypothesis that fertilization depends upon the attainment of the correct redox potential (which is a measure of the tendency a substance has to give up or to take up electrons) of the egg. The author noted a difference in potential between egg and sperm and the degree of this difference varied with the species. In some cases as in *Arbacia* it was considerable, whereas in other cases it was very slight as in *Asterias.*

The electromotively active enzyme systems required "activation" to produce the beginning of development. This meant that the concentration of oxidants and reductants must be more nearly equalized so that the electron shift could take place at an optimum rate, thereby releasing the necessary energy. In some cases as in *Asterias,* only a slight shift in potential was required. In others as *Arbacia,* there was a considerable change. This would explain why *Arbacia* eggs have a large rise in oxygen consumption on fertilization and *Asterias* eggs do not. The fact that eggs and sperm contain different proportions of these oxidants and reductants cause them to react.

The formation of acid upon fertilization of some eggs, whether by sperm or artificially, is an important factor and fitted the above theory that a change in pH of the egg produced a change in the redox potential. The increased production of carbon dioxide or other acids in the egg, caused by such various methods as sperm, hypertonic and hypotonic solutions, pricking, shaking or ultra violet light, was assumed by the author to be the cause of initiating development owing to changes in redox potential so produced.

When eggs were placed in sea water or modified sea water, they lowered the Eh and the pH (hydrogen in concentration). This lowering was more pronounced in modified sea water than in sea water. The redox potential of different species of eggs was different and changed with stages of development.

In conclusion Brooks states there was a definite correlation between the rate of oxygen consumption of unfertilized and fertilized eggs and the redox potential of these eggs. The three groups of eggs studied illustrated the hypothesis that fertilization of the egg depended upon the correct ratio of oxidants to reductants of the enzyme systems. C. E. FOLSOME.

Michelson, Lewis: Azoospermia: An Analysis of 146 Cases, J. Urol. **57:** 512-518, 1947.

Michelson presents an excellently documented and detailed analysis of 146 cases of azoospermia which had been most carefully studied.

In sixty-nine cases, 47 per cent, the etiology was determined; in seventeen cases, 11 per cent, the cause could be shown only unilaterally; in sixty patients, 41 per cent, this factor could not be determined.

The most frequent cause of degeneration of the spermatogenic cells was cryptorchidism, occurring in twelve cases, 8 per cent of the series. Mumps orchitis degenerative changes were seen in nine cases, 6 per cent of the series. The most frequent disease causing obstruction of the vaso-epididymal duct was gonorrhea. This occurred in thirty-five cases, or 24 per cent of the series.

Absence of both vasa was found in four cases. Testicular biopsy is deemed, by Michelson, as essential in diagnosis and determining treatment of azoospermia. His results of treatment were poor. He has seen not a single case show improvement after hormone therapy. In his hands only surgical measures have been successful and these are among the obstructive azoospermic cases. Three of eight cases showed sperm postoperatively and in two of these three cases the wife became pregnant. C. E. FOLSOME.

Labor

Strouse, Solomon, and Drabkin, Charles: Hyperthyroidism in Pregnancy Treated With Thiouracil, J. A. M. A. **131:** 1494, 1946.

The authors report a case of a 31-year-old primigravida with symptoms of hyperthyroidism following a thyroidectomy six years previously. The patient developed dyspnea, palpitation, tachycardia, and edema, and was placed on Lugol's solution, digitalis and sedatives with only fair results. She was then placed on thiouracil 0.6 Gm. daily and in one week she was feeling fine. She entered the hospital with ruptured membranes and a breech presentation. She was delivered by a low cervical section under spinal anesthesia. The post-operative course was uneventful. The baby gave the impression of being hypothyroid. The baby's subsequent development was perfectly normal. WILLIAM BERMAN.

Malignancies

Fremont-Smith, Maurice, Miegs, Joe V., Graham, Ruth M., and Gilbert, Helen H.: Cancer of the Endometrium and Prolonged Estrogen Therapy, J. A. M. A. **131:** 805, 1946.

The authors review the literature with reference to the carcinogenic effect upon the uterus and the breast with the continued use of estrogens. The authors report a case of endometrical cancer in a woman undergoing prolonged treatment with estrogen.

mg. of estrone sulfate, and 18 mg. of diethyl-stilbestrol, over a period of 8 years. This same patient had a positive diagnosis of endometrial hyperplasia two years prior to the discovery of her malignancy. The authors believe that this is the first report on the occurrence of endometrical cancer in a women undergoing prolonged treatment with estrogen.

WILLIAM BERMAN.

Howe, Martha E., and Jennings, Mary A.: Intrauterine Irradiation, A Modification of the Radiumhemmet Packing Method, J. A. M. Women's A. 2: 83, 1947.

In cases of cancer of the uterine body which are not treated surgically, one should deliver a maximal radiotherapeutic dose to the entire endometrium, and as deeply as possible into the uterine wall. In the irregular and distorted uterine cavity it is not possible to predetermine the location or extent of mucosal or myometrial extension.

Since radium needles in tandem are not likely to deliver efficient radiation, various methods of applicator distribution have been tried. In 1939 the Radiumhemmet group (Sweden) began to pack the uterus with numbers of tubular steel casings containing radium salt. This type of treatment has resulted in a 20 per cent improvement in five-year results in those cases which had treatment by radiation alone.

Howe and Jennings, of the New York Infirmary, have devised and used a new type of applicator. It is shaped like an olive pit, 20 mm. in length and 8 mm. in maximum diameter (one size only). It is closed by a screw cap bearing an eyelet for identifying tags. The shape permits penetration into the uterine cornu, close packing against neighboring applicators, and the shape minimizes weak radiation at the ends, since applicators can overlap. About ten applicators fill the uterus and cervical canal (dilatation of the cervix is maintained by the application in situ).

After insertion the patient is x-rayed to be sure that perforation has not occurred, and to demonstrate good distribution of applicators. A dose of 1,000 gamma roentgens is delivered at a depth of 1.5 cm. at each of three treatments, with one supplemental treatment to the vaginal vault and cervical portio by a vaginal applicator. The total dose to the uterus and vagina will vary from 3,300 to 6,000 milligram hours, depending on the size of these cavities. The total presumptive tumor dose, however, should be about the same in any case; about 3,000 gamma roentgens at 1.5 cm. depth and about 12,000 to 15,000 gamma roentgens at the endometrium. Experience with this method is limited as yet, and does not warrant conclusions as to its worth.

IRVING L. FRANK.

Anatomy

Swenson, Paul C.: Anatomic Variations in the Female Pelvis: The Caldwell-Moloy Classification, Radiology **827:** 1947.

In an editorial, Swenson discusses the paper of Nicholson and Allen (*Lancet* **2:** 192, 1946). These authors have criticized the Caldwell-Moloy classification for lack of precision, and for limitless subclassification and multiplication of types. They seek to disprove that anthropoid and android pelves are associated with narrow outlets, or that the android pelvis is associated with difficult labor. Caldwell and Moloy, however, did not present these as constant relationships. A large pelvis may not be dystocic whatever its shape, whereas in pelves of normal or borderline size, the pelvic form may be of prime importance.

Nicholson and Allen believe that all pelvic deformities are due to malnutrition in childhood, but Swenson indicates that nutrition affects only the general size of a predetermined (hereditary or hormonal influences) type. Emphasis on size alone will probably not be as valuable as the dynamic method of Caldwell-Moloy, which in its size-shape analysis has been of great aid to obstetricians.

IRVING L. FRANK.

Item

The following is inserted at the request of the Cutter Laboratories:

For Immediate Release

Berkeley, Calif.
May 6, 1948

Superseding our air mail release dated May 5, 1948 is the following statement from Dr. R. K. Cutter, president, of Cutter Laboratories. "Contamination has been found in another and entirely different glucose solution, dextrose 10 per cent in Ringer's, according to an announcement made today by Dr. R. K. Cutter, president, of Cutter Laboratories. The company is cooperating with the Food and Drug Administration, and is requesting the assistance of health departments throughout the country, in immediately recalling from hospitals Cutter's entire line of dextrose and other solutions for mass intravenous injection. Company officials believe that discovery of this new contamination makes questionable the use of any product produced in their intravenous solutions department until this entire contamination difficulty is solved. The other products produced in this department are concentrated dextrose, distilled water, sodium citrate, normal saline solutions in 50 and 100 c.c. bottles, as well as all flasks supplied by Cutter for community blood and plasma banks."

Announcement

In view of the many manuscripts submitted for publication in the JOURNAL, the number of pages in each issue will be increased to 200, beginning with the July number.

Necrology

HENRICUS JOHANNES STANDER, M.S., M.D., professor of obstetrics and gynecology at the Cornell Medical College and chief of the New York Lying-In Hospital, died at his home in Scarsdale, N. Y., on May 2, 1948, at the age of 53 years. Born in South Africa of Boer and English ancestry, he studied chemistry at the South African College and then at Harvard University, having arrived in the United States in 1913. He next was associated with the School of Mines of the University of Arizona, where he obtained his M.S. degree in 1916, and subsequently was a consulting chemist for the Hercules Powder Company at Wilmington, Del. Later, Dr. Stander entered the Yale Medical School and received his M.D. degree in 1921. He then became a member of the Department of Obstetrics of Johns Hopkins under the late Dr. J. Whitridge Williams. Subsequently he edited and enlarged Williams' well-known textbook on obstetrics and was the author of many articles in American medical journals. An honorary degree of Doctor of Medicine was awarded to him by the University of Dublin a year ago. Dr. Stander was a Fellow and member of the leading obstetrical societies of this country and for many years a member of the Advisory Medical Board of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

JOSIAH MORRIS SLEMONS, A.B., M.D., obstetrician and gynecologist, died in Los Angeles, Calif., on April 30, 1948, at the age of 71 years. A graduate of Johns Hopkins in 1901, he served there as instructor and associate professor of obstetrics, 1904 to 1913; as professor of obstetrics at the University of California, 1913 to 1915; as professor of obstetrics and gynecology in the Yale University Medical School, 1915 to 1920. During 1917, he was in charge of the survey of obstetrics in France under the sponsorship of the Red Cross and subsequently was a Major in the U.S.A. Medical Corps. He was the author of several books and numerous articles published in the JOURNAL. He lived in retirement at Los Angeles for several years.

INDEX TO VOLUME 55

AUTHORS INDEX*

A

ABEL, STUART, FARMER, CHESTER J., AND DOUCETTE, JEANNE, Observations on vaginal absorption of penicillin, 461

ADAMSON, D. L. (WITH WEAVER, R. T., AND JOHNSON, F. L.), Ovarian pregnancy, 437

ANDROS, G. J., DIECKMANN, WILLIAM J., OUDA, P., PRIDDLE, H. D., SMITTER, R. C., AND BRYAN, W. M., JR., Spinal (saddle block) anesthesia in obstetrics, 806

ARAGON, GLORIA T., An evaluation of plasma pitocinase determination in the toxemias of pregnancy, 961

ARNESON, A. N., STANBRO, WILLIAM W., AND NOLAN, JAMES F., The use of multiple sources of radium within the uterus in the treatment of endometrial cancer, 64

ASHTON, DOROTHY L., Carcinoma of the cervix complicating procidentia uteri, 299

B

BAER, JOSEPH L., Current teaching trends in obstetrics, 348

BARNES, ALLAN C., AND DOAN, CHARLES A., Splenectomy in pregnancy: its hematologic indications and obstetric management, 864

BENNETT, T. R. (WITH DIDDLE, A. W.), Carcinoma of the cervix in an urban population, 669

BENSON, RALPH C., The arrest of abnormal uterine bleeding with pitressin tannate in oil, 286

BICKERS, WILLIAM. Hysterosalpingography, 549 (Cor.)

BISKIND, MORTON S., Nutritional deficiency and menstrual disturbances, 360 (Cor.)

BOEDEKER, ROY V. (WITH VOGT, WILLIAM H., JR., AND LOPEZ, GUILLERMO), Uterine suspension, 1044

BOURNE, WESLEY, Wise indifference of the wise in anesthesia, 711

BRACKETT, EDWARD S., Retroversion of the uterus, 184 (Cor.)

BREWER, JOHN I., AND JONES, HAROLD O., Studies of the human corpus luteum, 18

BRODY, SIMON, Management of placenta previa, 359 (Cor.)

BROWN, WILLIS E., Single injection caudal for obstetrical analgesia and the use of Pontocaine, 717

BRYAN, W. M., JR. (WITH ANDROS, G. J., DIECKMANN, WILLIAM J., OUDA, P., PRIDDLE, H. D., AND SMITTER, R. C.), Spinal (saddle block) anesthesia in obstetrics, 806

BUSBY, TRENT, The duration of labor: mean, median, and mode, 846

BUSHNELL, LOWELL F., Endometriosis and estrogen therapy, 915 (Cor.)

C

CALDWELL, J. D. (WITH PUND, EDGAR R., NETTLES, J. B., AND NIEBURGS, H. E.), Preinvasive and invasive carcinoma of cervix uteri, 831

CAMPBELL, A. D., Our heritage and our stewardship (presidential address, American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, fifty-eighth annual meeting), 551

CARROLL, B. H., MEIER, H. H., AND STONE, O. H., Immediate postpartum hemorrhage due to retained secundines, 620

CARTER, BETTINA B. (WITH LOUGHREY, JOSEPH), The treatment of erythroblastosis fetalis with Rh hapten, 1051

CARTER, F. B. (WITH ROSS, ROBERT A., LAMBETH, S. S., AND THOMAS, W. L.), Fifty-four deaths occurring in pregnant patients who had hypertension, 591

COHEN, MELVIN R. (WITH STEIN, IRVING F., AND ELSON, RALPH), Sterilization failure with external migration of the ovum, 875

CORNELL, EDWARD L., Vaginal and rectal pruritus—etiology and treatment, 691

—, AND MULLEN, JOSEPH J., Early rising after delivery, 768

COUNSELLER, VIRGIL S., Diverticulitis: symptoms, complications, and management, particularly in the female, 653

COWIE, D. B. (WITH FLEXNER, L. B., HELLMAN, L. M., WILDE, W. S., AND VOSBURGH, G. J.), The permeability of the human placenta to sodium in normal and abnormal pregnancies and the supply of sodium to the human fetus as determined with radioactive sodium, 469

D

DAVIS, ALBERT, Induction of labor, 548 (Cor.)

DAY, LOIS A., MUSSEY, ROBERT D., AND DEVOE, ROBERT W., The intrauterine pack in the management of postpartum hemorrhage, 231

DEVOE, ROBERT W. (WITH DAY, LOIS A., AND MUSSEY, ROBERT D.), The intrauterine pack in the management of postpartum hemorrhage, 231

DIDDLE, A. W., AND BENNETT, T. R., Carcinoma of the cervix in an urban population, 669

DIECKMANN, WILLIAM J. (WITH ANDROS, G. J., OUDA, P., PRIDDLE, H. D., SMITTER, R. C., AND BRYAN, W. M., JR.), Spinal (saddle block) anesthesia in obstetrics, 806

— (WITH TALSO, PETER J.), Anemias of pregnacy, 518

—, AND HAUSER, ELIZABETH B., Pregnancy following tubal sterilization, 308

DOAN, CHARLES A. (WITH BARNES, ALLAN C.), Splenectomy in pregnancy: its hematologic indications and obstetric management, 864

DOUCETTE, JEANNE (WITH ABEL, STUART, AND FARMER, CHESTER J.), Observations on vaginal absorption of penicillin, 461

DOUGLASS, LOUIS H., AND GRAVES, JAMES H., Hysterostomatomy, 683

—, AND JORGENSEN, C. LOUIS, Pregnancy and multiple sclerosis, 332

DRIPS, DELLA G., Ovarian dysfunction in young women treated with low-dosage irradiation, 789

*January, pp. 1-188; February, pp. 189-366; March, pp. 367-550; April, pp. 551-732; May, pp. 733-916; June, pp. 917-1098.

DuBois, John C. (with Mackenzie, Locke L., Wetchler, Ben B., and Neustaedter, Theodore), The use of the vaginal smear in a gynecologic service, 821
DuShane, James W. (with Murphy, George H.), Mesodermal mixed tumor of the vagina: report of a case, 527

E

Eisaman, Josiah R. (with Fino, Julius A.), Combined local infiltration anesthesia and Pentothal sodium anesthesia in cesarean sections, 887
Ekas, Ward L. (with Wilson, Karl M., and Schultz, John H.), Advanced ectopic pregnancy, 218
Elson, Ralph (with Stein, Irving F., and Cohen, Melvin R.), Sterilization failure with external migration of the ovum, 875

F

Farmer, Chester J. (with Abel, Stuart, and Doucette, Jeanne), Observations on vaginal absorption of penicillin, 461
Findley, Palmer, Ignaz Philipp Semmelweis, 700
Fino, Julius A., and Eisaman, Josiah R., Combined local infiltration anesthesia and Pentothal sodium anesthesia in cesarean sections, 887
Flexner, L. B., Cowie, D. B., Hellman, L. M., Wilde, W. S. and Vosburgh, G. J., The permeability of the human placenta to sodium in normal and abnormal pregnancies and the supply of sodium to the human fetus as determined with radioactive sodium, 469
Fluhmann, C. F., A clinical and histopathologic study of lesions of the cervix uteri during pregnancy, 133
Ford, John C., The repeat cesarean, 183 (Cor.)
Fremont-Smith, Maurice, and Meigs, Joe V., Menstrual dysfunction due to emotional factors, 1037
Freundlich, Charles G. (with Hesseltine, H. Close, and Hite, K. Eileen), Acute puerperal mastitis, 778

G

Gardner, George H., Greene, R. R., and Peckham, B. M., Normal and cystic structures of the broad ligament, 917
Gifford, Houghton, and Hullinghorst, R. L., Poliomyelitis in pregnancy, 1030
Graham, Ruth M., Sturgis, Somers H., and McGraw, John, A comparison of the accuracy in diagnosis of the vaginal smear and the biopsy in carcinoma of the cervix, 303
Granger, G. A., Leunbach's paste, 364 (Cor.)
Grant, Kenneth M., Sterility in the female, 416
Graves, James H. (with Douglass, Louis H.), Hysterostomatomy, 683
Greeley, Arthur V. (with Speert, Harold), Cervical cancer with metastasis to breast, 894
Greenberg, Mervin W., Parotitis complicating the early puerperium, 340
Greene, R. R. (with Gardner, George H., and Peckham, B. M.), Normal and cystic structures of the broad ligament, 917
Grossbard, Paul (with Schmitz, Herbert E.), Endometriosis of episiotomy scar, 880

H

Haines, Samuel F. (with Mussey, Robert D., and Ward, Emmerson), Hyperthyroidism and pregnancy, 609
Harrison, J. E., Vaginal repair combined with vaginal hysterectomy, 403
Hartnett, Leo J., The possible significance of arterial visualization in the diagnosis of placenta previa, 940
Haultain, W. F. T., Now and then. A statistical review of the progress of midwifery during the last twenty years with thoughts for the future, 733
Hauser, Elizabeth B. (with Dieckmann, Wm. J.), Pregnancy following tubal sterilization, 308
Hellman, L. M. (with Flexner, L. B., Cowie, D. B., Wilde, W. S., and Vosburgh, G. J.), The permeability of the human placenta to sodium in normal and abnormal pregnancies and the supply of sodium to the human fetus as determined with radioactive sodium, 469
Herrick, F. L., Pentothal sodium anesthesia for cesarean sections, 883
Hertig, Arthur T. (with Rock, John), The human conceptus during the first two weeks of gestation, 6
Hesseltine, H. Close, Freundlich, Charles G., and Hite, K. Eileen, Acute puerperal mastitis, 778
Hindman, Daniel H., Pelvic delivery following cesarean section, 273
Hite, K. Eileen (with Hesseltine, H. Close, and Freundlich, Charles G.), Acute puerperal mastitis, 778
Hoffman, Jacob (with Scheffey, Lewis C., Rakoff, A. E., and Meyers, Dorothy), An evaluation of the vaginal smear method for the diagnosis of uterine cancer, 453
Holman, Albert W., and Schirmer, Elizabeth H., Factors in the treatment of chorionepithelioma, 629
Howson, John Y., Pelvic cancer delay (the organization and observations of the Philadelphia Committee for the Study of Pelvic Cancer), 538 (Special article)
Hudgins, A. P., Screw type cervical cannula, 549 (Cor.)
Huffman, John W., The detailed anatomy of the paraurethral ducts in the adult human female, 86
Hullinghorst, R. L. (with Gifford, Houghton), Poliomyelitis in pregnancy, 1030

I

Israel, S. Leon, and Mazer, Charles, Aspiration curettage, 365 (Cor.)

J

Jacox, Harold W. (with Johnston, James R.), Rectal hemorrhage following irradiation for carcinoma of cervix, 891
Johnson, C. Gordon, and Mayne, Ruth, Study of the incidence and occurrence of symptoms of vaginal trichomonads and various species of yeast in pregnancy, 852
Johnson, F. L. (with Weaver, R. T., and Adamson, D. L.), Ovarian pregnancy, 437
Johnston, H. W., An improved operative technique for salpingostomy, 426
Johnston, James R., and Jacox, Harold W., Rectal hemorrhage following irradiation for carcinoma of cervix, 891
Jones, Brock D. (with Kimbrough, Robert A.), Antepartum hemorrhage, 496
Jones, Harold O. (with Brewer, John I.), Studies of the human corpus luteum, 18
Jorgensen, C. Louis (with Douglass, Louis H.), Pregnancy and multiple sclerosis, 332

K

Kaiser, Irwin H., Histologic appearance of coiled arterioles in the endometrium of Rhesus monkey, baboon, chimpanzee, and gibbon, 699

KAREN, BENJAMIN, AND KUSHNER, J. IRVING, Dysgerminoma of the ovary, 337
KERR, MARION, A study of maternal mortality in Canada, 396
KIMBROUGH, ROBERT A., AND JONES, BROCK D., Antepartum hemorrhage, 496
KLAFTEN, EMANUEL, Culdoscopy, 1071 (Cor.)
KURCZ, JOSEPH A., AND SHARP, MAHLON S., Congenital absence of one ovary associated with contralateral tubal pregnancy, 1065
KUSHNER, J. IRVING (WITH KAREN, BENJAMIN), Dysgerminoma of the ovary, 337

L

LAMBETH, S. S. (WITH ROSS, ROBERT A., THOMAS, W. L., AND CARTER, F. B.), Fifty-four deaths occurring in pregnant patients who had hypertension, 591
LI, MIN HSIN, Malignant granulosa-cell tumor in an intrasplenic ovarian graft in a castrated male mouse, 316
LIGHT, FRANK P., A nine-year follow-up in cases of toxemia of pregnancy, 321
LOPEZ, GUILLERMO (WITH VOGT, WILLIAM H., JR., AND BOEDEKER, ROY V.), Uterine suspension, 1044
LOUGHREY, JOSEPH, AND CARTER, BETTINA B., The treatment of erythroblastosis fetalis with Rh hapten, 1051
LOVELADY, SIM B. (WITH MCELIN, THOMAS W., AND WOLTMAN, HENRY W.), Chorea gravidarum, 992
LUBIN, SAMUEL (WITH POLAYES, S. H., AND MCNALLY, JAMES, JR.), Antenatal blood group determination, 524
LUND, CURTIS J. Maternal congenital heart disease as an obstetric problem, 244
—, Newer obstetric analgesics, 1007
LYNN, HARVEY D. (WITH WHITACRE, FRANK E., AND MORRISON, DEMPSIE B.), Spectroscopic detection of hematin in the peripheral blood, 838

MC

MACARTHUR, J. L., Plasma proteins in pregnancy, 382
— (WITH WARD, C. V.), Blood platelet studies during pregnancy and the puerperium, 600
MCELIN, THOMAS W., LOVELADY, SIM B., AND WOLTMAN, HENRY W., Chorea gravidarum, 992
MCGRAW, JOHN (WITH GRAHAM, RUTH M., AND STURGIS, SOMERS H.), A comparison of the accuracy in diagnosis of the vaginal smear and the biopsy in carcinoma of the cervix, 303
MCLENNAN, CHAS. E., AND THOUIN, L. G., Blood volume in pregnancy, 189
MCNALLY, JAMES, JR. (WITH POLAYES, S. H., AND LUBIN, SAMUEL), Antenatal blood group determination, 524

M

MACKENZIE, LOCKE L., Cornification in the cervix and estrogenic activity, 913 (Cor.)
—, WETCHLER, BEN B., DUBOIS, JOHN C., AND NEUSTAEDTER, THEODORE, The use of the vaginal smear in a gynecologic service, 821
MAECK, J. VAN S., AND ZILLIACUS, H., Heparin in the treatment of toxemia of pregnacy, 326
MARBACH, A. HERBERT, A multiple sulfonamide therapeutic measure in the postoperative care of the cervix and vagina, 511
MARTIN, SHIRLEY (WITH PARKS, JOHN), Reactions of the vulva to systemic diseases, 117
MATARESE, A. A. (WITH TEDESCHI, C. G.), Benign trophoblastic cell proliferation, 758
MAYNE, RUTH (WITH JOHNSON, C. GORDON), Study of the incidence and occurrence of symptoms of vaginal trichomonads and various species of yeast in pregnancy, 852
MAZER, CHARLES (WITH ISRAEL, S. LEON), Aspiration curettage, 365 (Cor.)
MEIER, H. H. (WITH CARROLL, B. H., AND STONE, O. H.), Immediate postpartum hemorrhage due to retained secundines, 620
MEIGS, JOE V. (WITH FREMONT-SMITH, MAURICE), Menstrual dysfunction due to emotional factors, 1037
MEISTER, PETER C. (WITH SURAN, ROLAND R.), Papilloma of the cervix uteri in pregnacy, 342
MENDELSON, CURTIS L., Pulmonary embolism from amniotic fluid, 911 (Cor.)
MENGERT, WILLIAM F., Fetal and neonatal mortality: causes and prevention, 660
MENKIN, MIRIAM, AND ROCK, JOHN, In vitro fertilization and cleavage of human ovarian eggs, 440
MEYERS, DOROTHY (WITH SCHEFFEY, LEWIS C., RAKOFF, A. E., AND HOFFMAN, JACOB), An evaluation of the vaginal smear method for the diagnosis of uterine cancer, 453
MILES, LEE M. The elective use of Kielland forceps in management of occipitoposterior and occipitotransverse positions, 504
MITRA, SUBODH, The evaluation of the results of carcinoma of the cervix uteri treated by radical vaginal operation, 293
MONTGOMERY, JOHN B, Malignant tumors of the ovary, 201
MORRISON, DEMPSIE B. (WITH WHITACRE, FRANK E., AND LYNN, HARVEY D.), Spectroscopic detection of hematin in the peripheral blood, 838
MULLEN, JOSEPH J. (WITH CORNELL, EDWARD L.), Early rising after delivery, 768
MURPHY, GEORGE H., AND DUSHANE, JAMES W., Mesodermal mixed tumor of the vagina: report of case, 527
MUSSEY, ROBERT D. (WITH DAY, LOIS A., AND DEVOE, ROBERT W.), The intrauterine pack in the management of postpartum hemorrhage, 231
—, HAINES, SAMUEL F., AND WARD, EMMERSON, Hyperthyroidism and pregnancy, 609

N

NEIGUS, IRWIN (WITH WOLFE, SAMUEL A.), The effect of equine gonadotropin (Gonadogen) on the human ovary, 979
NETTLES, J. B. (WITH PUND, EDGAR R., CALDWELL, J. D., AND NIEBURGS, H. E.), Preinvasive and invasive carcinoma of cervix uteri, 831
NEUSTAEDTER, THEODORE (WITH MACKENZIE, LOCKE L., WETCHLER, BEN B., AND DUBOIS, JOHN C.), The use of the vaginal smear in a gynecologic service, 821
NIEBURGS, H. E. (WITH PUND, EDGAR R., NETTLES, J. B., AND CALDWELL, J. D.), Preinvasive and invasive carcinoma of cervix uteri, 831
NOLAN, JAMES F. (WITH ARNESON, A. N., AND STANBRO, WILLIAM W.), The use of multiple sources of radium within the uterus in the treatment of endometrial cancer, 64
NOVAK, EMIL, AND RUTLEDGE, FELIX. Atypical endometrial hyperplasia simulating adenocarcinoma, 46

O

OUDA, P. (WITH ANDROS, G. J., DIECKMANN, WILLIAM J., PRIDDLE, H. D., SMITTER, R. C., AND BRYAN, W. M., JR.), Spinal (saddle block) anesthesia in obstetrics, 806

P

PAGANO, ALPHONSE F., Ovarian dysgerminoma, 1058
PARKS, JOHN, AND MARTIN, SHIRLEY, Reactions of the vulva to systemic diseases, 117
— AND PUZAK, MICHAEL A., Influences of posture on the urinary tract in pregnancy, 636
PECKHAM, B. M. (WITH GARDNER, GEORGE H., AND GREENE, R. R.), Normal and cystic structures of the broad ligament, 917
PHANEUF, LOUIS E., Hysterectomy, 646
PHILPOTT, N. W., AND TWEEDIE, F. J., The baby as a problem in premature delivery, 481
PIERCE, ROBERT R., Penicillin vaginal suppositories and the prevention of postpartum morbidity, 313
PLASS, E. D., Drainage of a hydrocephalic head, 548 (Cor.)
POLAYES, S. H., LUBIN, SAMUEL, AND MCNALLY, JAMES, JR., Antenatal blood group determination, 524
POWER, R. M. H., Embryological development of the levator ani muscle, 367
PRIDDLE, H. D. (WITH ANDROS, G. J., DIECKMANN, WILLIAM J., OUDA, P., SMITTER, R. C., AND BRYAN, W. M., JR.), Spinal (saddle block) anesthesia in obstetrics, 806
PUND, EDGAR R., NETTLES, J. B., CALDWELL, J. D., AND NIEBURGS, H. E., Preinvasive and invasive carcinoma of cervix uteri, 831
PUZAK, MICHAEL A. (WITH PARKS, JOHN), Influences of posture on the urinary tract in pregnancy, 636
PYLE, LUCIEN R., Staphylococcus aureus hemolyticus puerperal mastitis and infections of the newborn, 676

R

RAKOFF, A. E. (WITH SCHEFFEY, LEWIS C., HOFFMAN, JACOB, AND MEYERS, DOROTHY), An evaluation of the vaginal smear method for the diagnosis of uterine cancer, 453
ROBERTSON, EDWIN M., High lymphadenectomy and sympathectomy in carcinoma of the vulva, 79
ROCK, JOHN (WITH MENKIN, MIRIAM F.), In vitro fertilization and cleavage of human ovarian eggs, 440
— AND HERTIG, ARTHUR T., The human conceptus during the first two weeks of gestation, 6
ROSE, DAVID, A modified method of surgical repair for prolapse of cervical stump with associated enterocele, 346
ROSS, ROBERT A., LAMBETH, S. S., THOMAS, W. L., AND CARTER, F. B., Fifty-four deaths occurring in pregnant patients who had hypertension, 591
RUCKER, M. PIERCE, Metallic sutures and early American gynecology (vice-president's address before American Gynecological Society, Seventieth Annual meeting, June 17-19, 1947), 1
RUTLEDGE, FELIX (WITH NOVAK, EMIL), Atypical endometrial hyperplasia simulating adenocarcinoma, 46
— (WITH TELINDE, RICHARD W.), Culdoscopy, a useful gynecologic procedure, 102

S

SCHADEL, LEES M., JR., A method of obstetric analgesia and anesthesia, 1016
SCHEFFEY, LEWIS C., RAKOFF, A. E., AND HOFFMAN, JACOB (WITH THE TECHNICAL ASSISTANCE OF MEYERS, DOROTHY), An evaluation of the vaginal smear method for the diagnosis of uterine cancer, 453
SCHIRMER, ELIZABETH H. (WITH HOLMAN, ALBERT W.), Factors in the treatment of chorionepithelioma, 629
SCHMITZ, HERBERT E., The treatment of cervix carcinoma with radium and 800 kilovolt x-ray, 262
— AND GROSSBARD, PAUL, Endometriosis of episiotomy scar, 880
— AND TOWNE, JANET E., The treatment of pelvic endometriosis, 583
SCHULTZ, JOHN H. (WITH WILSON, KARL M., AND EKAS, WARD L.), Advanced ectopic pregnancy, 218
SCHWARZ, OTTO H., AND WOOLF, RALPH B., Cervical dystocia, with special reference to the fibrous nature of the cervix, 151
SHARP, MAHLON S. (WITH KURCZ, JOSEPH A.), Congenital absence of one ovary associated with contralateral tubal pregnancy, 1065
SIEGLER, SAMUEL L., AND SILVERSTEIN, LOUIS M., Torsion of a pregnant uterus with rupture, 1053
SILVERSTEIN, LOUIS M. (WITH SIEGLER, SAMUEL L.), Torsion of a pregnant uterus with rupture, 1053
SMITH, JOSEPH T., Cesarean section scar, 1073 (Cor.)
SMITTER, R. C. (WITH ANDROS, G. J., DIECKMANN, WILLIAM J., OUDA, P., PRIDDLE, H. D., AND BRYAN, W. M., JR.), Spinal (saddle block) anesthesia in obstetrics, 806
SPECK, GEORGE, Phenolsulfonphthalein as a test for the determination of tubal patency, 1048
SPEERT, HAROLD, Late recurrence of cervical carcinoma following radiation therapy, 533
—, AND GREELEY, ARTHUR V., Cervical cancer with metastasis to breast, 894
STANBRO, WILLIAM W. (WITH ARNESON, A. N., AND NOLAN, JAMES F.), The use of multiple sources of radium within the uterus in the treatment of endometrial cancer, 64
STASHAK, THEO. S. (WITH WOLTZ, JOHN H. E.), A study of the use of penicillin in premature rupture of the membranes, 859
STEIN, IRVING F., COHEN, MELVIN R., AND ELSON, RALPH, Sterilization failure with external migration of the ovum, 875
STONE, O. H. (WITH CARROLL, B. H., AND MEIER, H. H.), Immediate postpartum hemorrhage due to retained secundines, 620
STROMME, WILLIAM B., True hermaphroditism, 1060
STURGIS, SOMERS H. (WITH GRAHAM, RUTH M., AND MCGRAW, JOHN), A comparison of the accuracy in diagnosis of the vaginal smear and the biopsy in carcinoma of the cervix, 303
SUN, KO-CHI, The characteristics in hysterosalpingograms in tuberculous salpingitis and endometritis, 953
SURAN, ROLAND R., AND MEISTER, PETER C., Papilloma of the cervix uteri in pregnancy, 342
SUTER, MAX, AND WICHSER, CELESTE, The fate of the living viable babies in extrauterine pregnancies, 489

T

TAFEL, RALPH E., TITUS, PAUL, AND WIGHTMAN, WILLIAM W. Hyaluronidase in treatment of human sterility, 1023
TALSO, PETER J., AND DIECKMANN, WILLIAM J., Anemias of pregnancy, 518
TEDESCHI, C. G., AND MATARESE, A. A., Benign trophoblastic cell proliferation, 758
TELINDE, RICHARD W., AND RUTLEDGE, FELIX, Culdoscopy, a useful gynecologic procedure, 102
THOMAS, W. L. (WITH ROSS, ROBERT A., LAMBETH, S. S., AND CARTER, F. B.), Fifty-four deaths occurring in pregnant patients who had hypertension, 591

THOUIN, L. G. (WITH MCLENNAN, CHAS. E.), Blood volume in pregnancy, 189
TITUS, PAUL (WITH TAFEL, RALPH E., AND WIGHTMAN, WILLIAM W.), Hyaluronidase in treatment of human sterility, 1023
TOWNE, JANET E. (WITH SCHMITZ, HERBERT E.), The treatment of pelvic endometriosis, 583
TRITES, ALBERT E., A study of breech delivery, 430
TWEEDIE, F. J. (WITH PHILPOTT, N. W.), The baby as a problem in premature delivery, 481

V

VOGT, WILLIAM H., JR., BOEDEKER, ROY V., AND LOPEZ, GUILLERMO, Uterine suspension, 1044
VOSBURGH, G. J. (WITH FLEXNER, L. B., COWIE, D. B., HELLMAN, L. M., AND WILDE, W. S.), The permeability of the human placenta to sodium in normal and abnormal pregnancies and the supply of sodium to the human fetus as determined with radioactive sodium, 469

W

WALSER, HOWARD C., Fear, an important etiological factor in obstetric problems, 799
WARD, C. V., AND MACARTHUR, J. L., Blood platelet studies during pregnancy and the puerperium, 600
WARD, EMMERSON (WITH MUSSEY, ROBERT D., AND HAINES, SAMUEL F.), Hyperthyroidism and pregnancy, 609
WARE, H. HUDNALL, JR., Observations on thirteen cases of late extrauterine pregnancy, 561
WEAVER, R. T., ADAMSON, D. L., AND JOHNSON, F. L., Ovarian pregnancy, 437
WETCHLER, BEN B. (WITH MACKENZIE, LOCKE L., DUBOIS, JOHN C., AND NEUSTAEDTER, THEODORE), The use of the vaginal smear in a gynecologic service, 821
WHITACRE, FRANK E., LYNN, HARVEY D., AND MORRISON, DEMPSIE B., Spectroscopic detection of hematin in the peripheral blood, 838
WICHSER, CELESTE (WITH SUTER, MAX), The fate of the living viable babies in extrauterine pregnancies, 489
WIGHTMAN, WILLIAM W. (WITH TAFEL, RALPH E., AND TITUS, PAUL), Hyaluronidase in treatment of human sterility, 1023
WILCOX, HOWARD L., Pregnancy following an interilio-abdominal amputation, 1068
WILDE, W. S. (WITH FLEXNER, L. B., COWIE, D. B., HELLMAN, L. M., AND VOSBURGH, G. J.), The permeability of the human placenta to sodium in normal and abnormal pregnancies and the supply of sodium to the human fetus as determined with radioactive sodium, 469
WILLIAMS, JOHN A., Leucemia and pregnancy, 967
WILLIAMS, TIFFANY J., The expectant management of placenta previa, 169
WILSON, KARL M., EKAS, WARD L., AND SCHULTZ, JOHN H., Advanced ectopic pregnancy, 218
WILSON, LEO, Estrogens in dysmenorrhea, 365 (Cor.)
WOLFE, SAMUEL A., AND NEIGUS, IRWIN, The effect of equine gonadotropin (Gonadogen) on the human ovary, 979
WOLTMAN, HENRY W. (WITH MCELIN, THOMAS, W., AND LOVELADY, SIM B.), Chorea gravidarum, 992
WOLTZ, JOHN H. E., AND STASHAK, THEO. S., A study of the use of penicillin in premature rupture of the membrane, 859
WOOLF, RALPH B. (WITH SCHWARZ, OTTO H.), Cervical dystocia, with special reference to the fibrous nature of the cervix, 151

Z

ZELLE, KANE, Arrhenoblastoma of the ovary, 869
ZILLIACUS, H. (WITH MAECK, J. VAN S.), Heparin in the treatment of toxemia of pregnancy, 326

SUBJECT INDEX*

A

Abortion induced by estrogens, placental changes in rabbit and (Sammartino and Blanchard), 725 (Abst.)
Abstracts, anatomy, 1084
cesarean section, 180
endocrinology, 181, 543, 724
endometriosis, 182, 904
fertility, 1082
gynecologic operations, 544, 726, 905
gynecology, 544, 725, 904
labor, 729, 906, 1083
malignancies, 178, 543, 724, 1084
mammary glands, 178
menopause, 545, 1076
newborn, 545, 727, 1077
pregnancy, 547, 728, 1079
puerperium, 908
sterility, 1082
toxemia, 547, 909, 1081
venereal disease, 729, 910
Adenocarcinoma, atypical endometrial hyperplasia simulating (Novak and Rutledge) 48
Airblock in newborn infant (Salmon et al), 1078 (Abst.)
American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, transactions of fifty-eighth annual meeting, 551
Board of Obstetrics and Gynecology, Inc., 186, 550, 732, 916 (Items)
Gynecological Society, transactions of seventieth annual meeting, June 17-19, 1947, 1, 189
Obstetrical and Gynecological Societies, roster of, 187, 730
Amniotic fluid, pulmonary embolism from (Mendelson), 911 (Cor.)
Analgesia and anesthesia, obstetric, method of (Schadel), 1016
obstetrical, single injection caudal for, and the use of Pontocaine (Brown), 717
Analgesics, obstetric, newer (Lund), 1007
Anatomic variations in female pelvis (Swenson), 1084 (Abst.)
Anatomy, 1084 (Absts.)
of paraurethral ducts in adult human female, detailed (Huffman), 86
Anemias of pregnancy (Talso and Dieckmann), 511
Anesthesia, combined local infiltration, and Pentothal sodium, in cesarean sections (Fino and Eisaman), 887
in cesarean section, problem of (Neme and Esteves), 180 (Abst.)
Pentothal sodium, for cesarean sections (Herrick), 883
spinal, as therapy in postpartum uterine atony (Hansen), 906 (Abst.)
saddle block, in obstetrics (Andros et al), 806
wise indifference of the wise in (Bourne), 711
Angioma of vulva (Alfieri), 904 (Abst.)
Antenatal blood group determination (Polayes et al), 524
Antepartum hemorrhage (Kimbrough and Jones), 496
Antigonadotropin formation following gonadotrophic hormone administration, further studies on (Leathem), 724 (Abst.)
Anti-Rh immunization, new biologic test to detect (Bessis), 727 (Abst.)
Arrhenoblastoma of ovary (Zelle), 869
Arterial visualization in diagnosis of placenta previa, possible significance of (Hartnett), 940
Aspiration curettage (Israel and Mazer), 365 (Cor.)
Avitaminosis E, chronic, in castrate and noncastrate rat (Martin), 727 (Abst.)
Azoospermia, an analysis of 146 cases (Michelson), 1083 (Abst.)

B

Babies, excessively large, pregnancy and labor in presence of (Amorin et al), 906 (Abst.)
living viable in extrauterine pregnancies, fate of (Suter and Wichser), 489
Baby in premature delivery, problem of (Philpott and Tweedie), 481
premature (Crosse), 900 (B. rev.)
Benign trophoblastic cell proliferation (Tedeschi and Matarese), 758
Bleeding, uterine, abnormal, endocrine factors and, during climacteric (Ingiulla), 1076 (Abst.)
arrest of abnormal, with pitressin tannate in oil, 286
Blood, anti-Rh immunization, new biologic test to detect (Bessis), 727 (Abst.)
group determination, antenatal (Polayes et al), 524
peripheral, hematin in, spectroscopic detection of (Whitacre et al), 838
platelet studies during pregnancy and puerperium (Ward and MacArthur), 600
postpartum, clotting mechanism and relationship to peripheral blood picture (Barnes), 908 (Abst.)
Rh, relation of, to congenital hemolytic disease and to intra-group transfusion reaction (Potter), 899 (B. rev.)
two popular fallacies regarding (Hattersley), 907 (Abst.)
volume in pregnancy (McLennan and Thouin), 189
Books, review of new, 351, 897
Breast and fallopian tube, carcinoma of, coexistent primary (Curran and Kilroy), 724 (Abst.)
cervical cancer with metastasis to (Speert and Greeley), 894
hypertrophy of, massive in pregnancy (Cusmano), 178 (Abst.)
Breech delivery, study of (Trites), 430
Broad ligament, normal and cystic structures of (Peckham et al), 917

C

Cancer cells, human, studies on chromosomes in (Barigozzi), 724 (Abst.)
cervical, colposcopy in early diagnosis of (Rocha), 179 (Abst.)
with metastasis to breast (Speert and Greeley), 894
cure of, causal, endogenous endocrinotherapy including (Samuel), 355 (B. rev.)
delay, pelvic (Howson), 538 (Special article)
diagnosis, treatment, prognosis (Ackerman), 900 (B. rev.)
endometrial, prolonged estrogen therapy (Fremont-Smith et al), 1084 (Abst.)
radium within uterus in treatment of, use of multiple sources of (Arneson et al), 64
uterine, diagnosis of, by use of vaginal smears, handbook for (Gates et al), 351 (B. rev.)
vaginal smear method for diagnosis of, evaluation of (Scheffey et al), 453

*January, pp. 1-188; February, pp. 189-366; March, pp. 367-550; April, pp. 551-732; May, pp. 733-916; June, pp. 917-1098.

Cannula, cervical, screw type (Hudgins), 549 (Cor.)
Carcinoma of cervix, accuracy in diagnosis of vaginal smear and biopsy in, comparison of (Graham et al), 303
and corpus uteri in young women (Bianchi), 179 (Abst.)
complicating procidentia uteri (Ashton), 299
follow-up study of 281 cases (Cusmano), 178 (Abst.)
in an urban population (Diddle and Bennett), 669
late recurrence of, following radiation therapy (Speert), 533
rectal hemorrhage following irradiation for (Johnston and Jacox), 891
treatment of, with radium and 800 kilovolt x-ray (Schmitz), 262
uteri, preinvasive and invasive (Pund et al), 831
treated by radical vaginal operation, evaluation of results of (Mitra), 293
of Fallopian tube and breast, coexistent primary (Curran and Kilroy), 724 (Abst.)
of isthmus, early primary (Cantone), 724 (Abst.)
of stump after suprovaginal hysterectomy (Cantone), 543 (Abst.)
of vulva, high lymphadenectomy and sympathectomy in (Robertson), 79
Cardiac patients during pregnancy, experience with (Aviles), 1080, (Abst.)
Cervical cancer with metastasis to breast (Speert and Greeley), 894
cannula, screw type (Hudgins), 549 (Cor.)
carcinoma, late recurrence of, following radiation therapy (Speert), 533
dystocia, with special reference to fibrous nature of cervix (Schwarz and Woolf), 151
stump, prolapse of, associated with enterocele, modified method of surgical repair for (Rose), 346
Cervix and vagina, postoperative care of, a multiple sulfonamide therapeutic measure in (Marbach), 511
carcinoma of, accuracy in diagnosis of vaginal smear and biopsy in, comparison of (Graham et al), 393
complicating procidentia uteri (Ashton), 299
follow-up study of 281 cases (Cusmano), 178 (Abst.)
in an urban population (Diddle and Bennett), 669
in young women (Bianchi), 179 (Abst.)
rectal hemorrhage following irradiation for (Johnston and Jacox), 891
treatment of, with radium and 800 kilovolt x-ray (Schmitz), 262
cornification in, and estrogenic activity (Mackenzie), 913 (Cor.)
fibrous nature of, cervical dystocia, with special reference to (Schwarz and Woolf), 151
infectious granulomatous lesions of (Guerriero et al), 726 (Abst.)
tuberculosis of (Casabona), 725 (Abst.)
uteri, carcinoma of, preinvasive and invasive (Pund et al), 831
treated by radical vaginal operation, evaluation of results of (Mitra), 293
lesions of, during pregnancy, clinical and histopathologic study of (Fluhmann), 133
papilloma of, in pregnancy (Suran and Meister), 342
Cesarean operations, anesthesia in, problem of (Neme and Esteves), 180 (Abst.)
section, 180 (Absts.)
abdominal drainage in unclean cases of (Peralta), 180 (Abst.)
anesthesia in, combined local infiltration and Pentothal sodium (Fino and Eisaman), 887
d-tubocurarine in (Gray), 180 (Abst.)
pelvic delivery following (Hindman) 273
Pentothal sodium anesthesia for (Herrick), 883
Cesarean section—Cont'd
peritoneal sulfonamide therapy during, at San Borja Maternity (Aguilo), 181 (Abst.)
scar (Smith), 1073 (Cor.)
the repeat (Ford), 183 (Cor.)
Childbirths, late second (Vara), 728 (Abst.)
Chorea gravidarum (McElin et al), 992
Chorionepithelioma, treatment of, factors in (Holman and Schirmer), 629
Chorionic infiltration, about so-called (De Giorgi), 1079 (Abst.)
Climacteric, endocrine factors and abnormal uterine bleeding during (Ingiulla), 1076 (Abst.)
Colposcopy in early diagnosis of cervical cancer (Rocha), 179 (Abst.)
Communicable diseases (Top), 902 (B. rev.)
Conceptus, human, during first two weeks of gestation (Rock and Hertig), 6
Congenital sincipital encephalocele and its treatment (Mustakallio), 546 (Abst.)
Corpus luteum, human, studies of (Brewer and Jones), 18
uteri, carcinoma of, in young women (Bianchi), 179 (Abst.)
Correspondence, 183, 184, 359, 548, 911, 1071
Cul-de-sac of Douglas, puncture of, importance of, in gynecology (Matus and Moreno), 544 (Abst.)
Culdoscopy (Klaften), 1070 (Cor.)
a useful gynecologic procedure (TeLinde and Rutledge), 102
Cystic structures of broad ligament (Peckham et al), 917

D

Delivery, breech, study of (Trites), 430
early rising after (Cornell and Mullen), 768
lochia following complete absence of (Heffernan and Sullivan), 907 (Abst.)
pelvic, following cesarean section (Hindman), 273
premature, baby as a problem in (Philpott and Tweedie), 481
Diarrhea of newborn, epidemic, in Massachusetts (Rubenstein and Foley), 1077 (Abst.)
what is, 1077 (Abst.)
Diverticulitis, symptoms, complications and management (Counseller), 653
d-Tubocurarine in cesarean section (Gray), 180, (Abst.)
Dysgerminoma of ovary (Karen and Kushner), 337
Dysmenorrhea, estrogens in (Wilson), 365 (Cor.)
Dystocia, cervical, with special reference to fibrous nature of cervix (Schwarz and Woolf), 151

E

Eclampsia, 541 (Editorial)
blood and bone marrow disorders associated with (Umberto), 547 (Abst.)
Ectopic endometrial tissue in thigh (Schlicke), 729 (Abst.)
pregnancy, advanced (Wilson et al), 218
Editorials, 177, 541
Eggs, fertilization of, mechanism of (Brooks), 1082 (Abst.)
Embryological development of levator ani muscle (Power), 367
Endocrine factors and abnormal uterine bleeding during climacteric (Ingiulla), 1076 (Abst.)
Endocrinology, 181, 543, 724 (Absts.)
female sex (Calatroni et al), 354 (B. rev.)
recent advances in (Cameron), 355 (B. rev.)
Endocrinotherapy, endogenous, including the causal cure of cancer (Samuel), 355 (B. rev.)
Endometrial cancer, radium within uterus in treatment of, use of multiple sources of (Arneson et al), 64
hyperplasia, atypical, simulating adenocarcinoma (Novak and Rutledge), 46
tissue, ectopic, in thigh (Schlicke), 729 (Abst.)

Endometriosis 182, 904 (Absts.)
a surgical problem (Macleod), 182 (Abst.)
and estrogen therapy (Bushnell), 915 (Cor.)
extragenital localization of (da Costa), 182 (Abst.)
of episiotomy scar (Schmitz and Grossbard), 880
pelvic, treatment of (Schmitz and Towne), 583
perforating fornix (Ahumada and Nogues), 904 (Abst.)
Endometritis, hysterosalpingograms in, characteristics in (Sun), 953
Endometrium, cancer of, and prolonged estrogen therapy (Fremont-Smith et al), 1084 (Abst.)
coiled arterioles in, histologic appearance of, in Rhesus monkey, baboon, chimpanzee, and gibbon (Kaiser), 699
Epidemic diarrhea of newborn, in Massachusetts (Rubenstein and Foley), 1077 (Abst.)
what is, 1077 (Abst.)
Episiotomy scar, endometriosis of (Schmitz and Grossbard), 880
Equine gonadotropin, effect of, on human ovary (Wolfe and Neigus), 979
Erythroblastosis fetalis, treatment of, with Rh hapten (Loughrey and Carter), 1051
Estrogen therapy, endometriosis and (Bushnell), 915 (Cor.)
prolonged, in cancer of endometrium (Fremont-Smith et al), 1084 (Abst.)
Estrogenic activity, cornification in cervix and (Mackenzie), 913 (Cor.)
Estrogens, abortion induced by, placental changes in rabbit and (Sammartino and Blanchard), 725 (Abst.)
in dysmenorrhea (Wilson), 365 (Cor.)
Excerpta medica (Woerdeman), 356 (B. rev.)
Extrauterine pregnancy, late, observations on thirteen cases of (Ware), 561
living viable babies in, fate of (Suter and Wichser), 489

F

Fallopian tube and breast, carcinoma of, coexistent primary (Curran and Kilroy), 724 (Abst.)
Fear, an etiological factor in obstetric problems (Walser), 799
Female, anatomy of paraurethral ducts in adult human (Huffman), 86
genitalia, tuberculosis of, concerning cases of (de Moraes and do Amaral), 544 (Abst.)
leucorrhea in (Restrepo), 353 (B. rev.)
pelvis, anatomic variations in (Swenson), 1084 (Abst.)
sex endocrinology (Calatroni et al), 354 (B. rev.)
sterility in (Grant), 416
Feminine psychology (Obregon de Maria), 358 (B. rev.)
Fertility, 1082 (Absts.)
Fetal and neonatal mortality, causes and prevention (Mengert), 660
Fetus, polycystic ovaries in (Bianchi), 1077 (Abst.)
Fevers, acute infectious (Joe), 902 (B. rev.)
Foot and ankle, injuries, diseases, deformities and disabilities (Lewin), 357 (B. rev.)
Forceps, Kielland, in management of occipitoposterior and occipitotransverse positions, elective use of, (Miles), 504
Friedman reaction in cerebrospinal fluid in diagnosis of hydatid mole (Garcia Huidobro and Paredes), 1080 (Abst.)

G

Genitalia, female, tuberculosis of, concerning cases of (de Moraes and do Amaral), 544 (Abst.)
Gestation, human conceptus during first two weeks of (Rock and Hertig), 6
Gonadogen, effect of, on human ovary (Wolfe and Neigus), 979
Gonadotrophic function of pituitary, influence of roentgen treatment upon (Baldins et al), 543 (Abst.)
hormone administration, antigonadotropin formation following, further studies on (Leathem), 724 (Abst.)
Gonadotropin, equine, effect of, on human ovary (Wolfe and Neigus), 979
Gonorrhea in women, penicillin in treatment of (Perkins and Brewster), 729 (Abst.)
Gravid uterus, retrodisplaced (Fouracre-Barns), 1080 (Abst.)
Gynecologic operations, 544, 726, 905 (Absts.)
practice, vaginal smear in (Mackenzie et al), 821
Gynecology, 544, 725, 904 (Absts.); 897 (B. rev.)
early American, metallic sutures and (Rucker), 1
functional surgery in (Bourg), 352 (B. rev.)
practical office (Karnaky), 351 (B. rev.)
puncture of cul-de-sac of Douglas in, importance of (Matus and Moreno), 544 (Abst.)
with section on female urology (Wharton), 352 (B. rev.)

H

Heart disease, maternal congenital, as obstetric problem (Lund), 244
Hematin in peripheral blood, spectroscopic detection of (Whitacre et al), 838
Hemorrhage, antepartum (Kimbrough and Jones), 496
following toxemia (Brouse), 910 (Abst.)
postpartum, immediate, due to retained secundines (Carroll et al), 620
intrauterine pack in management of (Day et al), 231
prolonged labor and (Odell et al), 729 (Abst.)
rectal, following irradiation for carcinoma of cervix (Johnston and Jacox), 891
Heparin in treatment of toxemia of pregnancy Maeck and Zilliacus), 326
Hermaphroditism, true (Stromme), 1060
Hormones, follicular and corpus luteum, pseudo-pregnancy picture induced by massive doses of (Szarka), 181 (Abst.)
maternal, influence of, on reproductive organs of suckling rats (Price), 181 (Abst.)
Human conceptus during first two weeks of gestation (Rock and Hertig), 6
corpus luteum, studies of (Brewer and Jones), 18
ovarian eggs, in vitro fertilization and cleavage of (Menkin and Rock), 440
placenta, permeability of, to sodium in normal and abnormal pregnancies and supply of sodium to human fetus as determined with radioactive sodium (Flexner et al), 469
Hyaluronidase in treatment of human sterility (Tafel et al), 1023
Hydatid mole, diagnosis of, Friedman reaction in cerebrospinal fluid in (Garcia Hufdobro and Paredes), 1080 (Abst.)
some considerations of (Cabrera), 1081 (Abst.)
Hydrocephalic head, drainage of (Plass), 548 (Cor.)
Hyperplasia, atypical endometrial, simulating adenocarcinoma (Novak and Rutledge), 46
Hypertension in pregnancy, cold pressor test in prediction of (Krieger and Weiden), 909 (Abst.)
menopausal, a critical study (Taylor), 545 (Abst.)
pregnant patients with, fifty-four deaths occurring in (Ross et al), 591
Hyperthyroidism in pregnancy (Mussey et al), 609
treated with thiouracil (Strouse and Drabkin), 1083 (Abst.)
Hypertrophy of breast, massive, in pregnancy (Cusmano), 178 (Abst.)

Hypervolemia secondary to grafted granulosa-cell tumor (Furth and Sobel), 543 (Abst.)
Hysterectomy, study based on 266 personal operations performed in 1945 and 1946 (Phaneuf), 646
supravaginal, carcinoma of stump after (Cantone), 543 (Abst.)
total, preservation of upper pelvic floor and bladder support in (Judd), 544 (Abst.)
vaginal, combined with vaginal repair (Harrison), 403
for nonmalignant conditions of uterus (da Silva Loureiro), 905 (Abst.)
report of experiences with (Stearns), 726 (Abst.)
Hysterosalpingograms, characteristics in, in tuberculous salpingitis and endometritis, (Sun) 953
Hysterosalpingography (Bickers), 549 (Cor.)
Hysterostomatomy (Douglas and Graves), 683

I

Ignaz Philipp Semmelweis (Findley), 700
Infants, newborn, airblock in (Salmon et al), 1078 (Abst.)
intravenous alimentation of (Dodd and Papoport), 1078 (Abst.)
vaginal smears in genital crisis of female (Tortora), 727 (Abst.)
Infertility in female, review of present position of investigation (Murless), 1082 (Abst.)
Interilio-abdominal amputation, pregnancy following (Wilcox), 1068
Intracranial damage in newly born (Nelson), 546 (Abst.)
Intraperitoneal sulfonamide therapy, prophylactic, in obstetric surgery (Perez and Echevaria), 908 (Abst.)
Intrauterine irradiation (Howe and Jennings), 1084 (Abst.)
pack in management of postpartum hemorrhage (Day et al), 231
Intravenous alimentation of infants (Dodd and Papoport), 1078 (Abst.)
therapy, study of (Massons), 357 (B. rev.)
In vitro fertilization and cleavage of human ovarian eggs (Menkin and Rock), 440
Irradiation, intrauterine (Howe and Jennings), 1084 (Abst.)
low-dosage, ovarian dysfunction in young women treated with (Drips), 789
Isthumus, carcinoma of, early primary (Cantone), 724 (Abst.)
Items, 186, 550, 732, 916, 1085

K

Kielland forceps in management of occipito-posterior and occipitotransverse positions, elective use of (Miles), 504

L

Labia, sudoriferous gland tumor on (De Giorgi), 905 (Abst.)
Labor, 729, 906, 1083 (Absts.)
duration of (Busby), 846
induction of (Davis), 548 (Cor.)
Pethidine in, results in 500 cases (Barnes), 907 (Abst.)
prolonged, and postpartum hemorrhage (Odell et al), 729 (Abst.)
puerperium, and newborn, pathology of (McCormick), 897 (B. rev.)
rupture of membranes before onset of (Tonkes), 906 (Abst.)
Lesions of cervix uteri during pregnancy, clinical and histopathologic study of (Fluhmann), 133
Leucemia and pregnancy (Williams), 967
Leucorrhea in female (Restrepo), 353 (B. rev.)
Leunbach's paste (Granger), 364 (Cor.)
Levator ani muscle, embryological development of (Power), 367
Liver in pregnancy, biopsy studies on (Ingerslev and Teilum), 1079 (Abst.)
Lochia following delivery, complete absence of (Heffernan and Sullivan), 907 (Abst.)
Lymphadenectomy, high, and sympathectomy in carcinoma of vulva (Robertson), 79

M

Malignancies, 178, 543, 724, 1084 (Absts.)
Mammary glands, 178 (Absts.)
Mastitis, acute puerperal (Hesseltine et al), 778
staphylococcus aureus hemolyticus puerperal, and infections of the newborn (Pyle), 676
Maternal mortality in Canada, study of (Kerr), 396
Membranes, rupture of, before onset of labor (Tonkes), 906 (Abst.)
Menopausal hypertension, a critical study Taylor et al), 545 (Abst.)
Menopause, 545, 1076 (Absts.)
Mesodermal mixed tumor of vagina, report of case (Murphy and DuShane), 527
Menstrual disturbances, nutritional deficiency and (Biskind), 360 (Cor.)
dysfunction due to emotional factors (Fremont-Smith and Meigs), 1037
Metabolism, diseases of (Duncan), 356 (B. rev.)
Metallic sutures and early American gynecology (Rucker), 1
Midwifery, statistical review of progress of, during last twenty years, with thoughts for the future (Haultain), 733
Multiple sclerosis, pregnancy and (Douglass and Jorgensen), 332

N

National Research Council, Committee on Human Reproduction, 732 (Item)
Necrology, Burnham, Curtis F., 186
Goodall, James R., 186
Meyer, Robert, 186
Rice, Frederick W., 916
Simpson, Frank Farrow, 542
Slemons, Josiah Morris, 1086
Stander, Henricus Johannes, 1086
Nephrogestosis, precursory symptoms of, and their importance for prognosis of parturition (Parviainen), 1081 (Abst.)
Newborn, 545, 727, 1077 (Absts.)
airblock in (Salmon et al), 1078 (Abst.)
diarrhea of, epidemic, in Massachusetts (Rubenstein and Foley), 1077 (Abst.)
what is, 1077 (Abst.)
dynamics of (Knop), 1078 (Abst.)
infections of, staphylococcus aureus hemolyticus puerperal mastitis and (Pyle), 676
intracranial damage in (Nelson), 546 (Abst.)
streptococcic sepsis of, from mastitis in pregnant mother (Fukas), 546 (Abst.)
weight and length of (Rossi), 545 (Abst.)
Nutritional deficiency and menstrual disturbances (Biskind), 360 (Cor.)

O

Obstetric analgesia and anesthesia, method of (Schadel), 1016
single injection caudal for, and the use of Pontocaine (Brown), 717
analgesics, newer (Lund), 1007
and Gynecologic Institute of Helsinki's University, annals of, 353 (B. rev.)
illustrations (Gerardo Will), 354 (B. rev.)
problem, fear, an etiological factor in (Walser), 799
maternal congenital heart disease as an (Lund), 244
surgery, prophylactic intraperitoneal sulfonamide therapy in (Perez and Echevarria), 908 (Abst.)

Obstetricians and Gynecologists of Canada, Society of, transactions of second annual meeting, 367
Obstetrics, 897 (B. revs.)
current teaching trends in (Baer), 348 (Special article)
early rising after delivery (Cornell and Mullen), 768
practical (Mayes), 354 (B. rev.)
spinal (saddle block) anesthesia in (Andros), 806
synopsis of (Litzenberg), 898 (B. rev.)
Occipitoposterior and occipitotransverse positions, Kielland forceps in management of, elective use of (Miles), 504
Ovarian dysfunction in young women treated with low-dosage irradiation (Drips), 789
dysgerminoma (Pagano), 1058
eggs, human, in vitro fertilization and cleavage of (Menkin and Rock), 440
graft, malignant granulosa-cell tumor in an intrasplenic, in a castrated male mouse (Li) 316
malignancy, primary (Campbell and Singman), 179 (Abst.)
pregnancy (Weaver et al), 437
Ovaries, polycystic, in fetus (Bianchi), 1077 (Abst.)
Ovary, arrhenoblastoma of (Zelle), 869
congenital absence of one, associated with contralateral tubal pregnancy (Kurcz and Sharp), 1065
dysgerminoma of (Karen and Kushner), 337
effect of equine gonadotropin (Gonadogen) on human (Wolfe and Neigus), 979
malignant tumors of (Montgomery), 201

P

Papilloma of cervix uteri in pregnancy (Suran and Meister), 342
Paraurethral ducts, anatomy of, in adult human female (Huffman), 86
Parotitis complicating early puerperium (Greenberg), 340
Parturition, prognosis of, precursory symptoms of nephrogestosis and their importance for (Parviainen), 1081 (Abst.)
Pathology of labor, puerperium, and Newborn (McCormick), 897 (B. rev.)
surgical (Boyd), 357 (B. rev.)
Pelvic cancer delay (Howson), 538 (Special article)
delivery following cesarean section (Hindman), 273
endometriosis, treatment of (Schmitz and Towne), 583
tumors associated with ascites and hydrothorax (Calmenson et al), 905 (Abst.)
Pelvis, female, anatomic variations in (Swenson), 1084 (Abst.)
Penicillin in premature rupture of membranes, study of use of (Woltz and Stashak), 859
in treatment of gonorrhea in women (Perkins and Brewster), 729 (Abst.)
therapy in acute puerperal mastitis (Hesseltine et al), 778
vaginal absorption of, observations on (Abel et al), 461
suppositories and prevention of postpartum morbidity (Pierce), 313
Pentothal sodium anesthesia and local infiltration anesthesia in cesarean sections (Fino and Eisaman), 887
for cesarean sections (Herrick), 883
Peripheral blood, hematin in, spectroscopic detection of (Whitacre et al), 838
Pethidine in labor, results in 500 cases (Barnes), 907 (Abst.)
Phenolsulfonphthalein as test for determination of tubal patency (Speck), 1048
Pituitary, gonadotrophic function of, influence of roentgen treatment upon (Baidins et al), 543 (Abst.)
Placenta, human, permeability of, to sodium in normal and abnormal pregnancies and supply of sodium to human fetus as determined with radioactive sodium (Flexner et al), 469
Placenta—Cont'd
previa, expectant management of (Williams), 169
diagnosis of, arterial visualization in, possible significance of (Hartnett), 940
management of (Brody), 359 (Cor.)
Placental toxin, active principle of (Schneider), 1081 (Abst.)
Plasma pitocinase determination in toxemias of pregnancy, evaluation of (Aragon), 961
proteins in pregnancy (MacArthur), 382
Poliomyelitis in pregnancy (Gifford and Hullinghorst), 1030
Polycystic ovaries in fetus (Bianchi), 1077 (Abst.)
Pontocaine, single injection caudal for obstetrical analgesia and the use of (Brown), 717
Postpartum blood, clotting mechanism and relationship to peripheral blood picture (Barnes), 908 (Abst.)
hemorrhage, immediate, due to retained secundines (Carroll et al), 620
intrauterine pack in management of (Day et al), 231
prolonged labor and (Odell et al), 729 (Abst.)
intraabdominal separation of uterus (Wassenaar), 908 (Abst.)
morbidity, penicillin vaginal suppositories and prevention of (Pierce), 313
Posture, influences of, on urinary tract in pregnancy (Parks and Puzak), 636
Pregnancies, extrauterine, living viable babies in, fate of (Suter and Wichser), 489
normal and abnormal, sodium in, permeability of human placenta to, and supply of, to human fetus as determined with radioactive sodium (Flexner et al), 469
Pregnancy, 547, 728, 1079 (Absts.)
advanced ectopic, (Wilson et al), 218
and labor in presence of excessively large babies (Amorin et al), 906 (Abst.)
and multiple sclerosis (Douglass and Jorgensen), 332
and puerperium, blood platelet studies during (Ward and MacArthur), 600
anemias of (Talso and Dieckmann), 511
blood volume in (McLennan and Thouin), 189
capillary fragility in (Gianaroli), 547 (Abst.)
cardiac patients during, experience with (Aviles), 1080 (Abst.)
contralateral tubal, congenital absence of one ovary associated with (Kurcz and Sharp), 1065
ectopic, advanced (Wilson et al), 218
extrauterine, late, observations on thirteen cases of (Ware), 561
following an interilio-abdominal amputation (Wilcox), 1068
tubal sterilization (Dieckmann and Hauser), 308
hypertension and toxemia in, cold pressor test in prediction of (Krieger and Weiden), 909 (Abst.)
death occurring in fifty-four patients with (Ross et al), 591
hyperthyroidism in (Mussey et al), 609
treated with thiouracil (Strouse and Drabkin), 1083 (Abst.)
lesions of cervix uteri during, clinical and histopathologic study of (Fluhmann), 133
leucemia and (Williams), 967
liver in, biopsy studies on (Ingerslev and Teilum), 728, 1079 (Absts.)
ophthalmoscopy study of eyeground in (Belvederi and Morano), 547 (Abst.)
ovarian (Weaver et al), 437
papilloma of cervix uteri in (Suran and Meister), 342
plasma pitocinase determination in toxemias of, evaluation of (Aragon), 961
proteins in (MacArthur), 382
poliomyelitis in (Gifford and Hullinghorst), 1030

Pregnancy—Cont'd
splenectomy in, hematologic indications and obstetric management (Barnes and Doan), 864
toxemia of, hemorrhage following (Brouse), 910 (Abst.)
heparin in treatment of (Maeck and Zilliacus), 326
late (Smith and Smith), 909 (Abst.)
nine-year follow-up in cases of (Light), 321
plasma pitocinase determination in, evaluation of (Aragon), 961
urinary tract in, influences of posture on (Parks and Puzak), 636
vaginal trichomonads and various species of yeast in, incidence and occurrence of symptoms of, study of (Johnson and Mayre), 852
vitamin A and carotene supplements of, during; effect on mother and newborn (Lewis et al), 1080 (Abst.)
Premature baby (Crosse), 900 (B. rev.)
delivery, baby as a problem in (Philpott and Tweedie), 481
Presidential address, American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, fifty-eighth annual meeting (Campbell), 551
Progesterone, pellets of, implantation of (de Santiago), 725 (Abst.)
Prolapse of cervical stump with associated enterocele, modified method of surgical repair (Rose), 346
Pruritus, vaginal and rectal, etiology and treatment (Cornell), 691
Psychiatry, modern attitudes in, 903 (B. rev.)
Psychology, feminine (Obregon de Maria), 358 (B. rev.)
Psychoneurogenic causes of sterility and their treatment (Rommer), 1082 (Abst.)
Puerperal mastitis, acute (Hesseltine et al), 778
staphylococcus aureus hemolyticus, and infections of newborn (Pyle), 676
Puerperium, 908 (Absts.)
blood platelet studies during (Ward and MacArthur), 600
early parotitis complicating (Greenberg), 340
Pulmonary embolism from amniotic fluid (Mendelson), 911 (Cor.)

R

Radium within uterus in treatment of endometrial cancer, use of multiple sources of (Arneson et al), 64
Rectal hemorrhage following irradiation for carcinoma of cervix (Johnston and Jacox), 891
Reproductive organs of suckling rats, influence of maternal hormones on (Price), 181 (Abst.)
Retrodisplaced gravid uterus (Fouracre-Barns), 1080 (Abst.)
Retroversion of uterus (Brackett), 184 (Cor.)
Rh hapten, treatment of erythroblastosis fetalis with (Loughrey and Carter), 1051
relation of, to congenital hemolytic disease and to intragroup transfusion reaction (Potter), 899 (B. rev.)
two popular fallacies regarding (Hattersley), 907 (Abst.)
Roster of American obstetrical and gynecological societies, 187, 730
Rupture of membranes, premature, use of penicillin in (Woltz and Stashak), 859

S

Saccharomyces in vaginal cycle (Cazzola and Mosconi), 1076 (Abst.)
Salpingitis, tuberculous, hysterosalpingograms in, characteristics in (Sun), 953
Salpingostomy, operative technique for, an improved (Johnston), 426
Semmelweis, Ignaz Philipp (Findley), 700
Sincipital encephalocele, congenital, and its treatment (Mustakallio), 546 (Abst.)
Society of Obstetricians and Gynecologists of Canada, transactions of second annual meeting, 367
Sodium, permeability of human placenta to, in normal and abnormal pregnancies and supply of, to human fetus as determined with radioactive sodium (Flexner et al), 469
Spinal (saddle block) anesthesia in obstetrics (Andros et al), 806
Splenectomy in pregnancy, hematologic indications and obstetric management (Barnes and Doan), 864
Sterility, 1082 (Absts.)
American Society for Study of, transactions of (1946), 353 (B. rev.)
and infertility in female, review of present position of investigation (Murless), 1082 (Abst.)
hyaluronidase in treatment of (Tafel et al), 1023
in female (Grant), 416
psychoneurogenic causes of, and their treatment (Rommer), 1082 (Abst.)
Sterilization failure with external migration of ovum (Stein et al), 875
tubal, pregnancy following (Dieckmann and Hauser), 308
Sudoriferous gland tumor on labia (De Giorgi), 905 (Abst.)
Sulfonamide therapeutic measure in postoperative care of cervix and vagina, a multiple (Marbach), 511
therapy, prophylactic intraperitoneal, in obstetric surgery (Perez and Echevaria), 908 (Abst.)
Supravaginal hysterectomy, carcinoma of stump after (Cantone), 543 (Abst.)
Sutures, metallic, and early American gynecology (Rucker), 1
Sympathectomy and high lymphadenectomy, in carcinoma of vulva (Robertson), 79
Syphilis, verification tests for, in office practice (Becker), 910 (Abst.)
Weltmann serum coagulation reaction in (Callaway), 910 (Abst.)

T

Thiouracil, hyperthyroidism in pregnancy treated with (Strouse and Drabkin), 1083 (Abst.)
Torsion of pregnant uterus with rupture (Siegler and Silverstein), 1053
Toxemia, 547, 909, 1081 (Absts.)
hemorrhage following, (Brouse), 910 (Abst.)
of pregnancy, cold pressor test in prediction of (Krieger and Weiden), 909 (Abst.)
heparin in treatment of (Maeck and Zilliacus), 326
late, (Smith and Smith), 909 (Abst.)
nine-year follow-up in cases of (Light), 321
plasma pitocinase determination in, evaluation of (Aragon), 961
Trichomonas vaginalis and trichomoniasis (Trussell), 897 (B. rev.)
Trophoblastic cell proliferation, benign (Tedeschi and Matarese), 758
Tubal patency, phenolsulfonphthalein as test for determination of (Speck), 1048
pregnancy, contralateral, congenital absence of one ovary associated with (Kurcz and Sharp), 1065
sterilization, pregnancy following (Dieckmann and Hauser), 308
Tuberculosis of cervix (Casabona), 725 (Abst.)
Tumor, grafted granulosa-cell, hypervolemia secondary to (Furth and Sobel), 543 (Abst.)
malignant granulosa-cell, in an intrasplenic ovarian graft in a castrated male mouse (Li), 316
mesodermal mixed, of vagina, report of case (Murphy and DuShane), 527
ovarian, malignant (Montgomery), 201

Tumor—Cont'd
sudoriferous gland, on labia (De Giorgi), 905 (Abst.)
Tumors, pelvic, associated with ascites and hydrothorax (Calmenson et al), 905 (Abst.)

U

Urinary tract in pregnancy, influences of posture on (Parks and Puzak), 636
Urology, female, gynecology with a section on (Wharton), 352 (B. rev.)
Uterine atony, postpartum, spinal anesthesia as therapy in (Hansen), 906 (Abst.)
bleeding, abnormal, arrest of, with pitressin tannate in oil (Benson), 286
endocrine factors and, during climacteric (Ingiulla), 1076 (Abst.)
cancer, diagnosis of, vaginal smear method, evaluation of (Scheffey et al), 453
suspension (Vogt et al), 1044
Uterus, cancer of, diagnosis of, by use of vaginal smears, handbook for (Gates et al), 351 (B. rev.)
intraabdominal separation of, postpartum (Wassenaar), 908 (Abst.)
nonmalignant conditions of, vaginal hysterectomy for (da Silva Loureiro), 905 (Abst.)
pregnant, torsion of, with rupture (Siegler and Silverstein), 1053
radium within, in treatment of endometrial cancer, use of multiple sources of (Arneson et al), 64
retrodisplaced gravid (Fouracre-Barns), 1080 (Abst.)
retroversion of (Brackett), 184 (Cor.)

V

Vagina, artificial, use of ovular membranes in creation of (Brindeau et al), 544 (Abst.)
mesodermal mixed tumor of, report of case (Murphy and DuShane), 527
Vagina—Cont'd
postoperative care of, a multiple sulfonamide therapeutic measure in (Marbach), 511
Vaginal absorption of penicillin, observations on (Abel et al), 461
and rectal pruritus, etiology and treatment (Cornell), 691
cycle, saccharomyces in (Cazzola and Mosconi), 1076 (Abst.)
hysterectomy combined with vaginal repair (Harrison), 403
for nonmalignant conditions of uterus (da Silva Loureiro), 905 (Abst.)
report of experiences with (Stearns), 726 (Abst.)
repair combined with vaginal hysterectomy (Harrison), 403
smear in genital crisis of female infants (Tortora), 727 (Abst.)
method for diagnosis of uterine cancer, evaluation of (Scheffey et al), 453
use of, in gynecologic practice (Mackenzie et al), 821
suppositories, penicillin, and prevention of postpartum morbidity (Pierce), 313
trichomonads and various species of yeast in pregnancy, incidence and occurrence of symptoms of, study of (Johnson and Mayne), 852
Venereal disease, 729, 910 (Absts.)
Vesicovaginal fistulas, incurable, treatment of (de Aquino Salles and Conri), 905 (Abst.)
Vitamin A intake, maternal, and ocular abnormalities in offspring, 546 (Abst.)
Vulva, angioma of (Alfieri), 904 (Abst.)
carcinoma of, high lymphadenectomy and sympathectomy in (Robertson), 79
reactions of, to systemic diseases (Parks and Martin), 117

W

Weltmann serum coagulation reaction in syphilis (Callaway), 910 (Abst.)